Title Page

Protocol Title:		A Phase 1, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 in Subjects of Chinese Descent With Advanced/Metastatic Solid Tumors With *KRAS p.G12C* Mutation (CodeBreaK 105)
Short Protocol Title:		AMG 510 Ethnic Sensitivity Study
Protocol Number:		20190147
Investigational Product:		AMG 510
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Data Elements Standards Version:		DES v6.2

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).

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 1, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 in Subjects of Chinese Descent With Advanced/Metastatic Solid Tumors With *KRAS p.G12C* Mutation (CodeBreaK 105), dated **05 January 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 subinvestigators (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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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 in Subjects of Chinese Descent With Advanced/Metastatic Solid Tumors With *KRAS p.G12C* Mutation (CodeBreaK 105)

Short Protocol Title: AMG 510 Ethnic Sensitivity Study

Study Phase: 1

Indication: Advanced/Metastatic Solid Tumors with *KRAS p.G12C* Mutation

Rationale

AMG 510 is a small molecule that specifically and irreversibly inhibits the Kirsten rat sarcoma viral oncogene homolog (KRAS)^{G12C} mutant protein. AMG 510 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 that covalently modifies the cysteine residue and locks KRAS^{G12C} in the inactive guanosine diphosphate (GDP)-bound conformation.

Preclinical studies of AMG 510 have demonstrated inhibition of growth and regression of cells and tumors harboring the *KRAS p.G12C* mutation. These data suggest that inhibition of KRAS^{G12C} may have therapeutic benefit for patients with *KRAS p.G12C*-driven cancers. The aim of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of AMG 510 in subjects of Chinese descent with advanced/metastatic solid tumors with the *KRAS p.G12C* mutation. The data from this study, in comparison with data from the global phase 1, first-in-human (FIH) study of AMG 510 (Study 20170543), will allow for an assessment of any ethnicity associated differences with AMG 510 treatment in subjects of Chinese descent, and subsequently enable China to participate in a global, phase 3 study of AMG 510.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of AMG 510 in adult subjects of Chinese descent with *KRAS p.G12C*-mutant advanced/metastatic solid tumors	• Subject incidence of dose-limiting toxicity (DLT), treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
• To characterize the pharmacokinetics (PK) of AMG 510 in subjects of Chinese descent when administered orally (PO)	• PK parameters of AMG 510 including, but not limited to, maximum observed plasma concentration (C_{max}), time to achieve C_{max} (t_{max}), and area under the plasma concentration time curve (AUC)
Secondary	
• To evaluate the preliminary efficacy of AMG 510 as a monotherapy in subsets of solid tumors with the *KRAS p.G12C* mutation	• Objective response, duration of response, progression-free survival (PFS), disease control, time to response (TTR), and duration of stable disease measured by computed tomography (CT) or magnetic resonance imaging (MRI) and assessed per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines

Overall Design

This is a non-randomized, open-label, multi-center phase 1 study to evaluate the safety, tolerability, PK, and preliminary efficacy of AMG 510 administered orally (PO) once daily (QD) in subjects of Chinese descent with *KRAS p.G12C*-mutant advanced/metastatic solid tumors. This study will be conducted at sites in Hong Kong and Taiwan.

Up to 18 subjects will be enrolled into the study. Enrollment into the first dose level cohort (cohort 1) may be from any eligible *KRAS p.G12C*-mutant advanced/metastatic solid tumor type. Six initial subjects will be enrolled into cohort 1 and will receive 960 mg of AMG 510 PO QD. If $\leq$ 1 dose-limiting toxicity (DLT) is observed in the first 6 subjects, up to 6 additional subjects may be enrolled in cohort 1 to collect additional PK, safety, and preliminary efficacy at the 960 mg dose. If $\geq$ 2 DLTs are observed in the first 6 subjects in cohort 1, an additional 6 subjects will be enrolled into a second dose level cohort (cohort 2), wherein the dose will be reduced to 720 mg AMG 510 PO QD. If $\leq$ 1 DLT is observed in the first 6 subjects in cohort 2, up to 6 additional subjects may be enrolled in cohort 2 to gather additional PK, safety, and preliminary efficacy at the 720 mg dose.

The safety and tolerability data from the first 6 subjects at the 960 mg dose level will be reviewed by a Dose Level Review Team (DLRT) 21 days after receiving the first dose of AMG 510. The DLRT will recommend whether cohort 1 should be continued at 960 mg or be modified and whether an additional 6 subjects could be enrolled in cohort 1 or if the 720 mg dose cohort (cohort 2) should be opened. If the DLRT makes the recommendation to enroll the next 6 subjects at the 720 mg AMG 510 dose in cohort 2, the DLRT will again review safety and tolerability data when the sixth enrolled subject at the 720 mg dose has the opportunity to receive AMG 510 for 21 days. The DLRT will recommend whether cohort 2 should be continued at 720 mg or be modified and whether an additional 6 subjects could be enrolled in cohort 2. The dose modification strategy for this study is described in Section 6.2.

Administration of AMG 510 may continue until there is evidence of disease progression, intolerance to study medication, or withdrawal of consent. Subjects will have a safety follow-up (SFU) visit approximately 30 (+7) days after the last dose of AMG 510 or before any new anticancer treatment is started, whichever occurs first. The SFU visit will be the end of study visit for each subject.

Number of Subjects

Up to 18 subjects will be enrolled in the study.

Summary of Subject Eligibility Criteria

Adult subjects (≥ 18 years old) with pathologically documented, previously treated, advanced/metastatic solid tumors will be eligible for this study. Enrollment will be restricted to subjects with advanced/metastatic solid tumors with the *KRAS p.G12C* mutation identified through local or central screening.

After providing informed consent, subjects will provide a medical history and undergo screening safety tests to confirm all eligibility requirements of the study have been met.

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

Treatments

AMG 510 PO QD will be administered daily for 21-day cycles, with no drug holidays between each cycle. The planned dose level(s) for AMG 510 will be dispensed at the research facility by a qualified staff member.

Procedures

Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed. After written informed consent has been obtained,

all screening tests and procedures will be performed within 28 days of administration of the first dose of AMG 510 (day 1), unless otherwise noted. **Any procedures, assessments, and laboratory tests obtained or performed as part of standard of care treatment prior to signing of informed consent may be used for screening requirements as long as they were within the allowed 28-day screening window prior to cycle 1 day 1.** Subjects will be seen in the clinic where clinical safety and study evaluations will be performed including physical examination, vital signs, clinical laboratory tests, electrocardiograms (ECGs), PK sample collections, and tumor imaging.

For a full list of study procedures, including the timing of each procedure, please refer to Section 8.2 and the Schedule of Activities in Table 1-1.

Statistical Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, and preliminary efficacy data by dose, and time as appropriate. 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.

The primary analysis will occur after all subjects (6 to 12 subjects) enrolled in cohort 1 and after all 6 to 12 subjects enrolled in cohort 2 (if $\geq$ 2 DLTs are observed in the first 6 subjects in cohort 1) have had the opportunity to complete 6 months on study or have been withdrawn from the study.

A final analysis is planned after all cohorts have ended the study. Primary and final analysis may be combined in case all subjects have ended study close to the time point of the primary analysis.

Listings of secondary efficacy endpoints will be produced for all subjects. The proportion of subjects with an objective response, defined as complete response (CR) + partial response (PR) (assessed per RECIST version 1.1) will be described. Additionally, the 95% CI will be tabulated by planned dose level, and similarly for subjects with disease control, defined as CR + PR + stable disease (SD) will be described. For all subjects treated at the planned dose, the Kaplan-Meier method will be used for time-to-event endpoints to estimate the survival curve, quartiles, and rates at selected timepoints with 95% CI for 1) duration of response, 2) progression-free survival, and 3) duration of stable disease. Event free rates at 3-month intervals will be estimated using the Kaplan-Meier method for progression-free survival (PFS). Time to response will be

summarized by the nonmissing sample size (n), standard deviation, median, minimum, and maximum for responders. Subject listings for time-to-event endpoints may be provided instead of Kaplan-Meier estimates or Clopper Pearson exact confidence interval if the analysis set has fewer than 10 subjects.

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

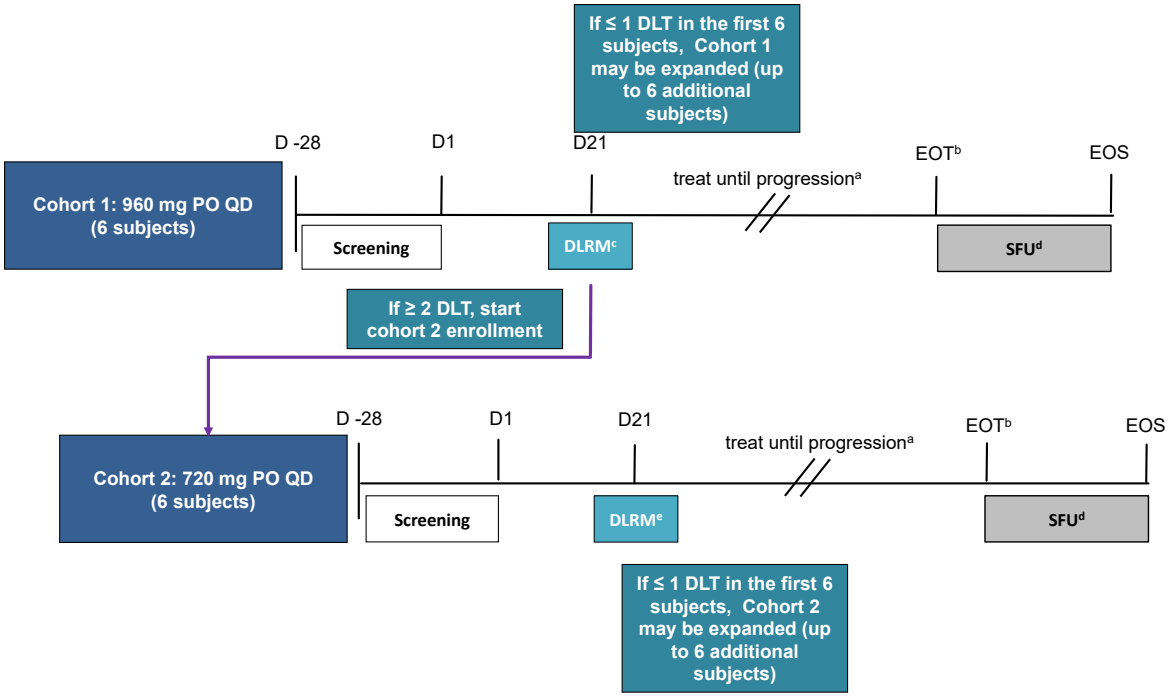
Statistical Hypotheses

No statistical hypothesis will be tested.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



DLRM = dose level review meeting; DLT = dose limiting toxicity; EOS = end of study; EOT = end of treatment; PO = orally; QD = once daily; SFU = safety follow-up.
[a] Administration of AMG 510 may continue until there is evidence of disease progression, intolerance to study medication, or withdrawal of consent.
[b] For subjects who discontinue investigational product, the EOT visit should occur as soon as possible (within 14 days) after the last dose of investigational product.
[c] The first DLRM will occur after the sixth study subject has received 21 days of AMG 510 in Cohort 1.
[d] The SFU visit should occur approximately 30 (+7) days after the last dose of AMG 510 or before any new anticancer treatment is started, whichever occurs first. The SFU visit will be the end of study visit for each subject.
[e] The second DLRM will occur after the sixth subject enrolled in Cohort 2 has received 21 days of AMG 510.

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities: Daily Dosing

	Screen[a]	Treatment																								EOT[b]	SFU[c]
Cycle		1															2					3,5 (± 2 days)	4,6 (± 2 days)	QC	Q2C		
Day	-28 to 1	1						2	8						9	15 (± 1 day)	1				8 (± 1 day)	1	1	1	1		
Hours (relative to dosing)		pre	0.25	0.5	1	2	4	6	pre	pre	0.25	0.5	1	2	4	6	pre	pre	pre	0.25	0.5	1	pre	pre	pre	pre	pre		
GENERAL & SAFETY ASSESSMENTS																													
Informed consent	X																												
Eligibility criteria	X																												
Demographics	X																												
Medical history & height	X																												
Smoking status	X																												
Physical exam & weight[d]	X	X							X							X	X					X	X	X			X		
ECOG[d]	X	X															X					X	X	X		X	X		
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X			X		
ECG[e, f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X			X		
Prior therapies	X																												

Footnotes defined following last page of the table

Table 1-1. Schedule of Activities: Daily Dosing

	Screen[a]	Treatment																									EOT[b]	SFU[c]
Cycle		1																2					3,5 (± 2 days)	4,6 (± 2 days)	QC	Q2C		
Day	-28 to 1	1						2	8						9	15 (± 1 day)	1				8 (± 1 day)	1	1	1	1		
Hours (relative to dosing)		pre	0.25	0.5	1	2	4	6	pre	pre	0.25	0.5	1	2	4	6	pre	pre	pre	0.25	0.5	1	pre	pre	pre	pre	pre		
GENERAL & SAFETY ASSESSMENTS (continued)																												
Concomitant medications		X	←==========																									
Adverse events			←==========																									
Serious adverse events[o]	←==========																											
Patient diaries			←==========																									
LABORATORY ASSESSMENTS																												
Chemistry[e]	X	X							X	X							X	X	X				X	X	X	X		X
HbA1c	X																											
Lipid panel[g]		X																					X			X		X
Thyroid panel[e]	X																	X					X	X	X			X
Hematology[e]	X	X							X	X							X	X	X				X	X	X	X		X
Coagulation[e]	X	X							X	X							X	X	X				X	X	X	X		X
Urinalysis[e, h]	X	X							X	X								X	X				X	X	X	X		X
Serum or urine pregnancy test[i]	X	X																	X				X	X	X			X

Footnotes defined following last page of the table

Table 1-1. Schedule of Activities: Daily Dosing

	Screen[a]	Treatment																										EOT[b]	SFU[c]
Cycle		**1**																**2**						**3,5 (± 2 days)**	**4,6 (± 2 days)**	**QC**	**Q2C**		
Day	**-28 to 1**	**1**							**2**	**8**						**9**	**15 (± 1 day)**	**1**				**8 (± 1 day)**	**1**	**1**	**1**	**1**		
Hours (relative to dosing)		**pre**	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**pre**	**pre**	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**pre**	**pre**	**pre**	**0.25**	**0.5**	**1**	**pre**	**pre**	**pre**	**pre**	**pre**		
LABORATORY ASSESSMENTS (continued)																													
Hepatitis serology	X																												
TUMOR SAMPLE (if *KRAS p.G12C* status is not known)																													
Archived tumor tissue (FFPE) or tumor biopsy	X[j]																												
IMAGING/EFFICACY ASSESSMENTS																													
Radiological imaging (CT/MRI) and tumor assessment[k, l]	X																							X			X	X	
MRI brain[l]	X																												
PK ASSESSMENTS																													
AMG 510 PK[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	(X)[m]				
STUDY DRUG ADMINISTRATION																													
AMG 510[n]			←==========→																										

Footnotes defined following last page of the table

CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FFPE = formalin-fixed paraffin-embedded; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; KRAS = Kirsten rat sarcoma; LDL = low-density lipoprotein; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics; PR = partial response; QC = every cycle from cycle 7 and beyond (cycles 7, 8, 9, etc), Q2C = every other cycle from cycle 7 and beyond (cycles 7, 9, 11, etc); RECIST = Response Evaluation Criteria in Solid Tumors;
Screen = screening; SFU = safety follow-up.
(X) = Parentheses indicate that the particular test is situational at that time point, as specified in the respective notes.

[a] *KRAS p.G12C* testing results must be available prior to starting all other screening procedures;

[b] For subjects who discontinue investigational product, the EOT visit should occur as soon as possible (within 14 days) after the last dose of investigational product.

[c] The SFU visit should occur approximately 30 (+7) days after the last dose of AMG 510 or before any new anticancer treatment is started, whichever occurs first. The SFU visit will be the end of study visit for each subject.

[d] Can be performed within a -1 day window (ie, 1 day prior to visit). **Height is only required at screening.**

[e] For laboratory assessments, every effort should be taken to perform assessments on the indicated study day. However, a window of ± 1 day is allowable for cycle 1 and cycle 2 (except for cycle 1 day 1 and cycle 1 day 8 where the window is -1 day). A window of ± 2 days is allowable after cycle 2. The same laboratory result should not be used for multiple assessments (for example using cycle 1 day 1 labs for both cycle 1 day 1 and cycle 1 day 2). For electrocardiograms and vital signs (including pulse oximetry): ± 5-minute window (for time points of 0.25 hr and 0.5 hr postdose), ± 15-minute window for all other postdose time points. On days of clinic visits, all predose assessments performed must be completed prior to dose administration (there is no allowance window, only that predose assessments must occur prior to dose administration).

[f] A single ECG must be performed at screening to fulfill inclusion criteria. In addition, 3 triplicate ECGs must be performed prior to the first dose of AMG 510 to serve as baseline. For all other visits, 1 triplicate ECG must be performed (See Section 8.2.3.2).

[g] Assessments to be performed on day 1 of every other cycle starting in cycle 3 (eg, C3, C5, C7, etc). Laboratory assessments may be performed within 24 hours before day 1 of cycle 1. **Lipid panel may include total cholesterol, HDL, and LDL depending on local standard practice for cholesterol testing, and triglycerides.**

[h] Microscopic exam to be performed **at the discretion of the investigator**.

[i] For female subjects of childbearing potential only. At screening, a highly sensitive serum pregnancy test is required. For all other time points, a highly sensitive serum or urine pregnancy test is required.

[j] If *KRAS p.G12C* status is not available in the subject's medical record, archived FFPE tissue (collected within 5 years) may be used for *KRAS p.G12C* screening by local or central testing (as applicable). If archived FFPE tissue is unavailable, a tumor biopsy may be performed.

[k] Radiological imaging and tumor assessments are required at screening and every 6 ± 1 weeks for the first 4 response assessments. After four 6-week response assessments, radiological imaging and tumor assessments will be performed every 12 ± 1 weeks. Imaging and tumor assessments will continue until disease progression, start of new anticancer treatment, death, withdrawal of consent, or until end of study. MRI/CT scans can be obtained earlier if clinical deterioration necessitates an earlier scan at the discretion of the managing physician. End of treatment CT/MRI should be performed only for subjects that discontinue treatment for a reason other than disease progression per RECIST 1.1 criteria. Every assessment must include the chest, abdomen, pelvis, and all other known sites of disease. Tumor burden assessments will be performed based on RECIST 1.1 guidelines (Section 11.8). Radiographic response (CR and PR) requires confirmation by a repeat assessment at least 4 weeks after the first detection of response.

[l] All subjects must have MRI of the brain performed within 28 days prior to enrollment. Only if MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain scans should be performed for all subjects with brain metastases or history of brain metastases and can also be performed at any time if clinically indicated or per standard of care. Any additional imaging used to evaluate or determine response (eg, PET, CT/PET, bone scan, etc) should be sent along with the required imaging to the central imaging vendor promptly upon completion.

[m] Pharmacokinetic blood samples should be collected at the exact nominal time point as noted above (see hour postdose column). If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. Pharmacokinetic samples not collected at exact nominal time point will not be considered protocol deviations. Predose PK samples should be performed prior to AMG 510 dosing. (X): only cycle 4 to be collected.

[n] AMG 510 will be administered daily on a repeated basis with no planned off treatment days. AMG 510 must be administered in the fasted state (no food or liquids, except water, 2 hours before to 1 hour after dosing) until cycle 2 day 2 and beyond at which time they may take AMG 510 with or without food.

[o] After end of study serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.2.4.1.3 for additional details.

2. Introduction

2.1 Study Rationale

AMG 510 is a small molecule that specifically and irreversibly inhibits the Kirsten rat sarcoma viral oncogene homolog (KRAS)^{G12C} mutant protein. AMG 510 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 that covalently modifies the cysteine residue and locks KRAS^{G12C} in the inactive guanosine diphosphate (GDP)-bound conformation.

Preclinical studies of AMG 510 have demonstrated inhibition of growth and regression of cells and tumors harboring the *KRAS p.G12C* mutation. These data suggest that inhibition of KRAS^{G12C} may have therapeutic benefit for patients with *KRAS p.G12C*-driven cancers. Accordingly, the first-in-human (FIH) Study 20170543 is evaluating the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of AMG 510 in subjects with *KRAS p.G12C*-mutant advanced non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and other solid tumors. The aim of this study is to evaluate the safety, tolerability, PK, and preliminary efficacy of AMG 510 in subjects of Chinese descent with advanced/metastatic solid tumors with the *KRAS p.G12C* mutation.

The data from this study, in comparison with data from the global phase 1, FIH study of AMG 510 (Study 20170543), will allow for an assessment of any ethnicity associated differences with AMG 510 treatment in subjects of Chinese descent, and subsequently enable China to participate in a global, phase 3 study of AMG 510.

2.2 Background

2.2.1 Disease

Advanced/metastatic cancer remains a leading cause of death for both men and women globally, with lung (small cell and non-small cell) and CRC among the most common causes of cancer death (WHO statistics, 2018). In 2018 there were approximately 234 030 new cases of lung cancer and 140 250 new cases of CRC in the United States alone (American Cancer Society, 2018). Despite significant progress over the last few decades, the prognosis for patients with advanced/metastatic solid tumors remains poor. The 5-year survival rates for advanced NSCLC and advanced CRC are approximately 5% and 14%, respectively (American Cancer Society, 2019). The poor prognosis in patients with advanced/metastatic solid tumors highlights a critical unmet medical need.

The KRAS guanosine triphosphate (GTP)-ase is involved in cell signalling pathways that regulate growth, division, and differentiation. A relationship between KRAS mutations and oncogenesis has been established in cancers with solid tumors such as NSCLC and CRC (Smith et al, 2010; Der et al, 1982;). Specifically, the *KRAS p.G12C* point mutation encodes an oncoprotein product with a structural change that prevents the association of GTPase-activating proteins, thereby reducing the hydrolysis of GTP by KRAS. Accumulation of the constitutively active, GTP-bound form of KRAS results in enhanced proliferative and survival signaling in tumor cells (Jones et al, 2017).

AMG 510 is being developed by Amgen Inc., a for profit pharmaceutical company. AMG 510 (sotorasib) was granted accelerated approved by the United States Food and Drug Administration (FDA) for the treatment of adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy.

Subjects with metastatic or unresectable NSCLC, CRC, and other solid tumors **(including pancreatic, endometrial, bladder, ovarian, endometrial, appendiceal, ampullary, and small intestine) with the *KRAS* *p.G12C*** mutation **are commonly** treated with combinations of chemotherapy, immunotherapy**,** or antiangiogenic agents. **In NSCLC, until recently, most subjects with a *KRAS p.G12C* mutation would have received platinum containing doublets, typically cisplatin/pemetrexed as standard first line options (NCCN, 2018), followed by second line therapy with a taxane with or without a vascular endothelial growth factor (VEGF) inhibitor.**

Amgen has initiated a global phase 1, FIH study of AMG 510 (Study 20170543) to evaluate the safety, tolerability, PK, and preliminary efficacy of orally-administered (PO) AMG 510 in adult subjects with *KRAS p.G12C*-mutant advanced solid tumors. To permit China's future participation in AMG 510 clinical development, including an anticipated phase 3 study, the aim of this study is to evaluate the safety, tolerability, PK, and preliminary efficacy of AMG 510 in subjects of Chinese descent with advanced/metastatic solid tumors with the *KRAS p.G12C* mutation. This study may be amended to include sites in China and seamlessly expand to phase 2 to further evaluate anti-tumor efficacy of AMG 510 in subjects of Chinese descent.

2.2.2 Amgen Investigational Product Background: AMG 510

AMG 510 is a small molecule that specifically and irreversibly inhibits the $KRAS^{G12C}$ oncoprotein encoded by the *KRAS p.G12C* mutation. AMG 510 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 the inactive GDP-bound conformation. This blocks the normal interaction between KRAS and the rapidly accelerated fibrosarcoma (RAF) protein kinase, and consequently prevents downstream signaling events including the phosphorylation of extracellular signal-regulated kinase (ERK) (Simanshu et al, 2017; Ostrem et al, 2013).

2.2.2.1 AMG 510 Preclinical Experience

In vitro, AMG 510 inhibited son-of-sevenless homolog 1 (SOS1)-catalyzed nucleotide exchange of recombinant mutant $KRAS^{G12C/C118A}$ (half-maximal inhibitory concentration [IC_{50}] = 0.09 µM), but had minimal effect on $KRAS^{C118A}$ (KRAS protein with a C118A mutation at the protein level), which is wildtype at G12. AMG 510 inhibited $KRAS^{G12C}$ signaling only in *KRAS p.G12C*-mutant cell lines tested. AMG 510 also impaired viability in all but one *p.G12C*-mutant cell line (IC_{50} values from 0.004 to 0.032 µM), but did not affect the viability of cell lines with other mutations in *KRAS* or with mutations in genes other than *KRAS*. The kinetic efficiency of AMG 510, defined as the rate of enzyme inactivation divided by the inhibitory constant for reversible enzyme inhibition, was within the reported range of values for covalent epidermal growth factor receptor (EGFR) inhibitors. In vivo pharmacodynamic analyses demonstrated that covalent modification of $KRAS^{G12C}$ by AMG 510 tracked with inhibition of ERK1/2 phosphorylation. Maximal inhibition and modification occurred within 2 to 4 hours and significant inhibition and modification of $KRAS^{G12C}$ persisted for 48 hours after a single dose of AMG 510. In tumor xenograft studies, AMG 510 significantly inhibited the growth of *KRAS p.G12C* tumors at doses as low as 3 mg/kg and achieved near complete regression at 100 mg/kg. Notably, AMG 510 had no effect in non-*KRAS p.G12C* tumor xenografts and did not affect body weight in any study.

2.2.2.2 Pharmacokinetics

AMG 510 exhibited moderate to high clearance and moderate volume of distribution at steady state in mice, rats, dogs, and cynomolgus monkeys. The terminal half-life associated with λ_z ($t_{1/2,z}$) of the compound in all the test species ranged between 0.34 and 0.71 hours. Following AMG 510 PO as a suspension or solution, the time to reach maximum observed plasma concentration (t_{max}) of AMG 510 was observed between 0.25 and 1.2 hours across the species tested. The oral bioavailability ranged from 3.3% to 47% across the species tested. The in vivo elimination of AMG 510 in nonclinical species suggests oxidative and conjugative metabolism as the primary routes

of elimination. AMG 510 has a potential to cause cytochrome P450 (CYP)3A-mediated drug-drug interactions (DDI) due to reversible and time-dependent inhibition of CYP3A, and induction of CYP3A4 in vitro. The M24 metabolite (AMG3368167) also has the potential to contribute to CYP3A-mediated DDI. The potential for AMG 510 to cause transporter-mediated DDIs is low except for multidrug and toxin extrusion protein 1 (MATE1) transport inhibition. In vitro, AMG 510 was shown to be a substrate of P-glycoprotein (P-gp) but not of breast cancer resistance protein (BCRP).

2.2.2.3 Toxicology

Nonclinical, repeat-dose toxicology studies of 7- and 28-day duration have been completed in the rat and dog at daily doses of AMG 510 up to 300 mg/kg. The key AMG 510-related finding of concern consisted of kidney tubular epithelial degeneration/necrosis which occurred in the rat only. In the 28-day rat study, renal tubular injury partially reversed after a 28-day recovery period, with evidence of ongoing resolution/repair; however, a few tubules were surrounded by fibroplasia. Additional findings were reversible and included increased spleen weight (rat only), increased leukocytes (rat only) and a decrease in red blood cell (RBC) mass (hemoglobin, RBC count, and hematocrit) that was associated with changes in reticulocytes and RBC indices. There were no AMG 510-related changes in either the rat or dog repeat-dose toxicology studies that were considered severely toxic; thus, the severely toxic dose in 10% (STD_{10}) in rats was $>$ 200 mg/kg and the highest nonseverely toxic dose (HNSTD) in dogs was $\geq$ 300 mg/kg.

The 3-month dog and rat toxicology studies did not identify any new target organs compared to the previous 1-month studies. In rats, the same renal change progressed to a chronic change that involved more of the renal tubule and was attributed to higher exposures and longer dosing duration. The STD_{10} in the rat was 180 mg/kg. In dogs, AMG 510-related changes including minimal to mild changes in hematology and clinical chemistry parameters, abnormal content in the gall bladder, and microscopic changes in the liver, pituitary, or thyroid were considered to be either non-severely toxic and/or adaptive or secondary responses to hepatocellular enzyme induction. No renal toxicity was identified in the dog. The HNSTD in the dog was 1000 mg/kg/day.

Mean observed AMG 510 clinical exposures from 180, 360, 720, and 960 mg once daily (QD) dosing in subjects were lower than the exposures observed at the STD_{10} of 180 mg/kg in rats in the 3-month Good Laboratory Practice (GLP) repeated-dose

toxicology study, but similar to or higher than the exposures observed at the HNSTD of 1000 mg/kg/day in dogs in the 3-month GLP repeated-dose toxicology study.

AMG 510 preclinical safety studies have not identified cardiovascular, respiratory, or nervous system concerns. Genotoxicity studies indicate an absence of significant genotoxic risk for AMG 510. AMG 510 was not phototoxic in vitro.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AMG 510 is provided in the AMG 510 Investigator's Brochure.

2.3 Benefit/Risk Assessment

Based on preclinical data, nonclinical toxicity studies, and the clinical experience with AMG 510, the overall benefit/risk profile favors clinical development of AMG 510 for subjects with *KRAS p.G12C*-driven cancers.

As of 17 July 2019, 76 subjects with *KRAS p.G12C* advanced or metastatic tumors were enrolled in the study. Of these 76 subjects, 34 (44.7%) had NSCLC, 35 (46.0%) had CRC, and 7 (9.2%) had other solid tumors. Fifty-five subjects were evaluable (ie, had 6-week response data or early progression). Of the 55 enrolled subjects with all cancer types who were evaluable, 13 subjects had partial response (PR) and 34 subjects had stable disease; the response was not evaluable for 1 subject.

Based on nonclinical toxicity studies of AMG 510, the key safety information to be monitored in clinical studies includes renal toxicity, anemia, leukocytosis, **thyroid abnormalities,** and splenomegaly. Based on clinical study data, the key **risks** to be monitored includes increases of AST and ALT**, and interstitial lung disease (ILD)/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.

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 AMG 510.

COVID-19 Related Benefit/Risk Assessment

Amgen closely monitors the coronavirus disease-2019 (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 AMG 510 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.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of AMG 510 in adult subjects of Chinese descent with *KRAS p.G12C*-mutant advanced/metastatic solid tumors	• Subject incidence of dose-limiting toxicity (DLT), treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
• To characterize the pharmacokinetics (PK) of AMG 510 in subjects of Chinese descent when administered orally (PO)	• PK parameters of AMG 510 including, but not limited to, maximum observed plasma concentration (C_{max}), time to achieve C_{max} (t_{max}), and area under the plasma concentration time curve (AUC)
Secondary	
• To evaluate the preliminary efficacy of AMG 510 as a monotherapy in subsets of solid tumors with the *KRAS p.G12C* mutation	• Objective response, duration of response, progression-free survival (PFS), disease control, time to response (TTR), and duration of stable disease measured by computed tomography (CT) or magnetic resonance imaging (MRI) and assessed per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines

4. Study Design

4.1 Overall Design

This is a non-randomized, open-label, multi-center phase 1 study to evaluate safety, tolerability, PK, and preliminary efficacy of AMG 510 PO QD in subjects of Chinese descent with *KRAS p.G12C*-mutant advanced/metastatic solid tumors. This study will be conducted at sites in Hong Kong and Taiwan.

Up to 18 subjects will be enrolled into the study. Enrollment into the first dose level cohort (cohort 1) may be from any eligible *KRAS p.G12C*-mutant advanced/metastatic solid tumor type. Six initial subjects will be enrolled into cohort 1 and will receive 960 mg of AMG 510 PO QD. If $\leq$ 1 dose-limiting toxicity (DLT) is observed in the first 6 subjects, up to 6 additional subjects will be enrolled in cohort 1 to collect additional PK, safety, and preliminary efficacy at the 960 mg dose. If $\geq$ 2 DLTs are observed in the first 6 subjects in cohort 1, an additional 6 subjects may be enrolled into a second dose level cohort (cohort 2), wherein the dose will be reduced to 720 mg AMG 510 PO QD. If $\leq$ 1 DLT is observed in the first 6 subjects in cohort 2, up to 6 additional subjects may be enrolled in cohort 2 to gather additional PK, safety, and preliminary efficacy at the 720 mg dose.

The safety and tolerability data from the first 6 subjects at the 960 mg dose level will be reviewed by a Dose Level Review Team (DLRT) 21 days after receiving the first dose of AMG 510. The DLRT will recommend whether cohort 1 should be continued at 960 mg or be modified and whether an additional 6 subjects could be enrolled in cohort 1 or if the 720 mg dose cohort (cohort 2) should be opened. If the DLRT makes the recommendation to enroll the next 6 subjects at the 720 mg AMG 510 dose in cohort 2, the DLRT will again review safety and tolerability data when the sixth enrolled subject at the 720 mg dose has the opportunity to receive AMG 510 for 21 days. The DLRT will recommend whether cohort 2 should be continued at 720 mg or be modified and whether an additional 6 subjects could be enrolled in cohort 2. The dose modification strategy for this study is described in Section 6.2.

Administration of AMG 510 may continue until there is evidence of disease progression, intolerance to study medication, or withdrawal of consent. Subjects will have a safety follow-up (SFU) visit approximately 30 (+7) days after the last dose of AMG 510 or before any new anticancer treatment is started, whichever occurs first. The SFU visit will be the end of study visit for each subject.

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

4.2 Number of Subjects

Up to 18 subjects will be enrolled in the study.

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

4.2.1 Replacement of Subjects

For the purpose of assessing the primary endpoints, subjects may be replaced if they withdraw from the study prematurely. A subject who discontinues from the study for reasons other than DLT after receiving investigational product may be replaced at the discretion of Amgen in consultation with the investigator or their designee.

4.2.2 Number of Sites

Approximately 2 to 4 investigative sites in Hong Kong and Taiwan will be included in the study. Sites that do not enroll subjects within 6 months of site initiation may be closed.

4.3 Justification for Investigational Product Dose

In the global phase 1/2 study of AMG 510 (Study 20170543), mean observed clinical exposures from 180, 360, 720, and 960 mg QD dosing in subjects were lower than the

exposures observed at the STD_{10} of 180 mg/kg in rats in the 3-month GLP repeated-dose toxicology study, but similar to or higher than the exposures observed at the HNSTD of 1000 mg/kg/day in dogs in the 3-month GLP repeated-dose toxicology study, (see the Investigator's Brochure). At these exposures, no DLTs were observed in subjects.

A dose level review meeting (DLRM) was held on 27 June 2019 to review the available safety and preliminary anti-tumor activity of AMG 510 in all subjects as of the 12 June 2019 data cut off. Following review of the aggregate safety data for all subjects and the available anti-tumor activity and PK data in Study 20170543, the Principal Investigators and the Amgen voting members unanimously agreed to propose 960 mg daily as the recommended phase 2 dose (RP2D). Thus, the 960 mg PO QD dose is considered to be safe and well tolerated and is proposed as the clinical starting dose of AMG 510 for this phase 1 study in subjects of Chinese descent. The proposed de-escalated dose for this study of 720 mg PO QD (if applicable) is one dose level below the 960 mg RP2D; based on available data from Study 20170543, this dose is also expected to be safe and tolerable in subjects of Chinese descent.

4.4 End of Study

4.4.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s).

The study-specific primary completion date is the date when the last subject has completed the assessments for the SFU visit.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: 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), following any additional parts in the study, as applicable.

4.4.2 Study Duration for Subjects

Subject participation in this study is expected to last approximately 1 year and includes a 28-day screening period and an estimated 6 to 12 months of treatment. However, this may vary depending on tolerability and response to treatment.

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). **However, any procedures, assessments, and laboratory tests obtained or performed as part of standard of care prior to signing of informed consent may be used for screening requirements as long as they were performed within the allowed 28-day screening window prior to cycle 1 day 1.**

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

102 Male or female subjects ≥ 18 years old

103 Subject is of Chinese ancestry (ie, both parents and 4 grandparents are/were of Chinese descent; it is not a necessity for the subject, the subject's parents, or grandparents to be born and raised in Hong Kong/Taiwan to participate in this study).

104 Pathologically documented, advanced/metastatic solid tumor with *KRAS p.G12C* mutation identified through local or central screening.

- For NSCLC: subjects must have received anti-programmed cell death protein 1 (PD-1) or anti-programmed death-ligand 1 (PD-L1) immunotherapy (unless contraindicated) and/or platinum-based combination therapy and targeted therapy (if actionable oncogenic driver mutations were identified [ie, EGFR, ALK, and ROS1]).
- For CRC: subjects must have received at least 2 prior systemic regimes for advanced or metastatic CRC including fluoropyrimidine, oxaliplatin, and irinotecan-based regimens. For those CRC subjects with tumors that are microsatellite instability-high (MSI-H), at least 1 of the prior systemic regimens must have included an anti-PD-1 therapy if they were clinically able

to receive inhibitors and 1 of these agents is approved for that indication in the region or country.

- For advanced/metastatic solid tumor types other than NSCLC or CRC: subjects must have received at least 1 prior systemic therapy or be intolerant or ineligible for available therapies known to provide clinical benefit.
- If *KRAS p.G12C* status is not available in the subject's medical record, an archived formalin-fixed paraffin-embedded (FFPE) tissue (collected within 5 years) may be used for *KRAS p.G12C* screening by local or central testing (as applicable). If archived tissue is not available, a tumor biopsy may be performed.

105 Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria

106 Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2

107 Life expectancy of $>$ 3 months, in the opinion of the investigator

108 Ability to take oral medications and willing to record daily adherence to investigational product utilizing a sponsor-provided dosing diary

109 Corrected QT interval (QTc) $\leq$ 470 msec for females and $\leq$ 450 msec for males

110 Adequate hematological laboratory assessments, as follows:

- absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
- platelet count $\geq 75 \times 10^9$/L
- hemoglobin $\geq$ 9 g/dL (90 g/L)

111 Adequate renal assessments, as follows:

- estimated glomerular filtration rate based on Modification of Diet in Renal Disease (MDRD) calculation $\geq$ 60 mL/min/1.73 m^2

112 Adequate hepatic laboratory assessments, as follows:

- aspartate aminotransferase (AST) $<$ 2.5 x upper limit of normal (ULN) (if liver metastases are present, $\leq$ 5 x ULN)
- alanine aminotransferase (ALT) $<$ 2.5 x ULN (if liver metastases are present, $\leq$ 5 x ULN)
- total bilirubin (TBL) $<$ 1.5 x ULN ($<$ 2.0 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)

113 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 or within target range if on prophylactic anticoagulation therapy

5.2 Exclusion Criteria

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

201 Active brain metastases from non-brain tumors. Subjects who have had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to study day 1 are eligible if they meet all of the following criteria: a) residual neurological symptoms grade $\leq$ 2; b) on stable doses of dexamethasone for at least 2 weeks, if applicable; and c) follow-up magnetic resonance imaging (MRI) performed within 30 days shows no new lesions appearing

202 History or presence of hematological malignancies unless curatively treated with no evidence of disease $\geq$ 2 years

203 Myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association $>$ class II), unstable angina, or cardiac arrhythmia requiring medication

204 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)

205 Active infection requiring IV antibiotics within 1 week of study enrollment (day 1)

206 Exclusion 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 needs exclusion).
- Positive Hepatitis C virus antibody: Hepatitis C virus RNA by polymerase chain reaction is necessary. Detectable Hepatitis C virus RNA suggests chronic hepatitis C and renders the subject ineligible

207 Known positive for human immunodeficiency virus (HIV)

208 Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade 0 or 1, or to levels dictated in the eligibility criteria with the exception of alopecia (grade 2 or 3 toxicities from prior anti-tumor therapy that are considered irreversible [defined as having been present and stable for $>$ 6 months], such as ifosfamide related proteinuria, 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)

209 Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, hormonal therapy [except for subjects with breast cancer], or investigational agent) within 28 days of study day 1; concurrent use of hormone deprivation therapy for hormone-refractory prostate cancer or breast cancer is permitted

210 Therapeutic or palliative radiation therapy within 2 weeks of study day 1. Subjects must have recovered from all radiotherapy-related toxicity.

211 Currently enrolled in another investigational device or drug study, or less than 28 days since ending another investigational device or drug study(s), or receiving other investigational agent(s)

212 Other investigational procedures are excluded

213 Major surgery within 28 days of study day 1

214 Female subjects of childbearing potential who are unwilling to use 1 highly effective method of contraception during treatment of AMG 510 and for an additional 7 days after receiving the last dose of AMG 510. Refer to Section 11.5 for additional contraceptive information.

215 Female subjects who are lactating/breast feeding or who plan to breastfeed while on study and for an additional 7 days after receiving the last dose of study drug

216 Female subjects with a positive pregnancy test assessed at screening by a highly sensitive serum pregnancy test

217 Female subjects planning to become pregnant while on study and for an additional 7 days after receiving the last dose of AMG 510

218 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 AMG 510. Refer to Section 11.5 for additional contraceptive information.

219 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 AMG 510

220 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 7 days after the last dose of AMG 510

221 Subject has known sensitivity to any of the products to be administered during dosing

222 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge

223 Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures

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

225 Use of known CYP3A4 and P-gp-sensitive 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

227 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.

228 History of other malignancy within the past 2 years, with the following exceptions:

- Malignancy treated with curative intent and with no known active disease present for $\geq$ 2 years before enrollment and felt to be at low risk for recurrence by the treating physician.

- 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 non-invasive carcinoma or carcinoma in situ without evidence of disease.

229 Previous treatment with a $KRAS^{G12C}$ inhibitor

230 Leptomeningeal disease

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 and in/on the enrollment electronic case report form (eCRF).

Each subject who enters into the screening period for the study receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned manually. 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.

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, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened **up to 2 times**. Refer to Section 8.1.1.

6. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, **combination product,** 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.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment (Table 6-1).

6.1 Treatment(s) Administered

6.1.1 Investigational Products

Table 6-1. Study Treatments

Study Treatment Name	Amgen Investigational Product:[a] AMG 510
Dosage Formulation	120 mg tablets
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	960 mg QD, or 720 mg QD if dose modification is required (See Section 6.2)
Route of Administration	Oral
Accountability	The planned dose, start date/time, stop date, quantity administered, unit, planned frequency, reason for dose change/withheld, package lot number to be recorded on each subject's eCRF(s).
Dosing Instructions	AMG 510 will be administered orally QD for 21-day cycles, with no drug holidays between each cycle. The planned dose level(s) for AMG 510 will be dispensed at the research facility by a qualified staff member. Subjects are required to take AMG 510 at the research facility on clinic visit days as described in Table 1-1. Subjects will take AMG 510 at home on non-clinic visit days at approximately the same time(s) every day. The AMG 510 dose should also not be taken more than 2 hours earlier than the **target** time **based on previous day's dose.** AMG 510 must be administered in the fasted state (no food or liquids, except water, 2 hours before to 1 hour after dosing) until cycle 2 day 2 and beyond at which time they may take AMG 510 with or without food. Subjects will receive AMG 510 with approximately 240 mL (8 ounces) of water. **The AMG 510 dose should not be taken more than 6 hours after the dosing time. Take the next dose as prescribed the next day. If vomiting occurs after taking AMG 510, do not take an additional dose. Take the next dose as prescribed the next day.** **Administration to patients who have difficulty swallowing solids: disperse tablets in 120 mL (4 ounces) of non-carbonated, room-temperature water without crushing. No other liquids should be used. Stir until tablets are dispersed into small pieces (the tablets will not completely dissolve) and drink immediately or within 2 hours. The appearance of the mixture may range from pale yellow to bright yellow. Swallow the tablet dispersion. Do not chew pieces of the tablet. Rinse the container with an additional 120 mL (4 ounces) of water and drink. If the mixture is not consumed immediately, stir the mixture again to ensure that tablets are dispersed.**

eCRF = electronic case report form; QD = once daily.

[a] AMG 510 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Non-investigational Products

There will be no non-investigational products administered 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 for this study.

6.1.5 Other Treatment Procedures

Not applicable to the 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(s) or device(s) 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 packing drug containers, delivery systems, labeling, and inserts.**

This includes any investigational products provisioned and/or repackaged/modified by Amgen. AMG 510 is the investigational product in this study.

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

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

The following medications and supplements to be avoided for 14 days prior to enrollment and during the study period unless reviewed and approved by the Principal Investigator and the Amgen Medical Monitor:

- Known strong inducers of CYP3A4 including herbal supplements, such as St. John's wort
- Known CYP3A4 and P-gp-sensitive substrates with a narrow therapeutic window **unless approved by Amgen medical monitor**
- **Proton pump inhibitors (PPI) and H2-receptor antagonists unless approved by Amgen medical monitor**

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 AMG 510. 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, AMG 510 must be discontinued, and the investigator or designee should notify the sponsor as soon as possible. A subject may be allowed to resume AMG 510 only if both the investigator and Amgen Medical Monitor agree to restart study therapy.

6.2 Dose Modification

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

Dose Level Determination

Up to 18 subjects will be enrolled into the study to evaluate the safety, tolerability, PK, and preliminary efficacy of AMG 510 PO QD in subjects of Chinese descent with *KRAS p.G12C*-mutant advanced/metastatic solid tumors. Enrollment into the first dose level cohort (cohort 1) may be from any eligible *KRAS p.G12C*-mutant advanced/metastatic solid tumor type. Six initial subjects will be enrolled into cohort 1 and will receive 960 mg of AMG 510 PO QD. If ≤ 1 DLT (defined in Section 6.2.2) is observed in the first 6 subjects, up to 6 additional subjects may be enrolled in cohort 1 to collect additional PK, safety, and preliminary efficacy at the 960 mg dose. If ≥ 2 DLTs are observed in the first 6 subjects in cohort 1, an additional 6 subjects may be enrolled into a second dose level cohort (cohort 2), wherein the dose will be reduced to 720 mg AMG 510 PO QD. If ≤ 1 dose-limiting toxicity (DLT) is observed in the first 6 subjects in cohort 2, up to 6 additional subjects may be enrolled in cohort 2 to gather additional PK, safety, and preliminary efficacy at the 720 mg dose.

After 6 DLT evaluable subjects in cohort 1 and after 6 DLT evaluable subjects in cohort 2 (if applicable) have completed the 21-day DLT window, a DLRM will be held to review data, monitor safety, and to provide recommendations related to dose change and further enrollment. If the DLRT makes the recommendation to enroll the next 6 subjects at the 720 mg AMG 510 dose in cohort 2, the DLRT will again review safety and tolerability data when sixth enrolled subject at the 720 mg dose has the opportunity to receive AMG 510 for 21 days. The DLRT will recommend whether cohort 2 should be continued at 720 mg or be modified and whether an additional 6 subjects could be enrolled in cohort 2. Dose level recommendations will be made on a treatment cohort basis (not on an individual basis). After receiving the DLRT recommendation, Amgen will render a final decision and will issue a written notification of the dose change and enrollment decision to investigators. Further information on DLRMs is provided in Section 11.3.

Dose Cohort Stopping Rules

The DLRT will recommend stopping or modifying dosing if suspected adverse drug reactions, changes in vital signs, electrocardiogram (ECG), or clinical laboratory results are observed, and these changes pose a significant health risk. The Amgen Medical Monitor may suspend dosing and convene a DLRM at any time based on emerging safety data.

Clinically or medically significant suspected adverse drug reactions, and serious adverse events considered to be related to study procedures will be followed until resolved or considered stable.

The study may be terminated at any point at the discretion of the sponsor.

6.2.2 Dose-limiting Toxicity Definition

A DLT is defined as any adverse event meeting the criteria listed below occurring during the first treatment cycle of AMG 510 (day 1 through day 21) where a relationship to AMG 510 cannot be ruled out.

The grading of adverse events will be based on the guidelines provided in the CTCAE (version 5.0). A DLT is defined as any of the following events during the first treatment cycle and attributable to AMG 510:

- Hematological toxicity
  - febrile neutropenia
  - neutropenic infection

  - grade 4 neutropenia
  - grade ≥ 3 thrombocytopenia for > 7 days
  - grade 3 thrombocytopenia with grade ≥ 2 bleeding
  - grade 4 thrombocytopenia
  - grade 4 anemia

- Non-hematological toxicity
  - grade ≥ 4 vomiting or diarrhea
  - grade 3 diarrhea or grade 3 vomiting lasting more than 3 days despite optimal medical support
  - grade ≥ 3 nausea for 3 days or more despite optimal medical support
  - any other grade ≥ 3 adverse event

Dose-limiting toxicity-evaluable is defined as completion of 80% of AMG 510 doses within the first treatment cycle (ie, 21 days). A subject who experiences a DLT within the first cycle is DLT-evaluable regardless of number of doses taken. If a subject is withdrawn from the study for any reason other than a DLT prior to completion of the 21-day safety observation period, a replacement subject (if applicable) will be assigned the same dose as the replaced subject.

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

6.2.3.1 Amgen Investigational Product: AMG 510

Subjects experiencing any treatment-related toxicity meeting the DLT definition will not receive additional AMG 510 treatment and will be followed until resolution of the event or toxicity. Subjects will be withdrawn from AMG 510 treatment and will be treated as deemed appropriate by the investigator or treating physician. In subjects who received the 960 mg dose level with a favorable response to treatment, an option to continue at the same dose level or the lower dose of 480 mg according to the dose modification guidelines in Table 6-2 can be considered.

The reason for dose modification of AMG 510 is to be recorded on each subject's eCRF. Dose reduction levels of AMG 510 for toxicity management of individual subjects are provided in Table 6-2. Up to 2 dose reductions are allowed. Dose reductions below 240 mg are not allowed.

Table 6-2. Dose Decrements for AMG 510

AMG 510 Doses (mg QD)		
Starting Dose	Dose -1	Dose -2
960	480	240

QD = once daily

AMG 510 will be discontinued, or dosage reduced in the event of toxicity that, in the opinion of the investigator, warrants the discontinuation, or dose reduction as indicated in Table 6-3. Subjects who experience an adverse event requiring dose reductions below 240 mg should be permanently discontinued from AMG 510 treatment.

If day 1 of a cycle is delayed, day 1 of subsequent cycles should be adjusted accordingly to maintain the 21-day cycle duration. However, if a within-cycle dose is held the missed dose will not be made up and day 1 of subsequent cycles should not be adjusted.

Table 6-3. AMG 510 Dose Modification Guidelines for Hematologic and Non-hematologic 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	**ILD/pneumonitis confirmed or excluded**	• **If confirmed, permanently discontinue AMG 510** • **If excluded, restart at same dose if no other AMG 510 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] Subjects may be resumed at a dose lower than the recommended restarting dose after discussion with the medical monitor.
[b] For suspected hepatotoxicity, refer to Section 6.2.4 and Section 11.7.

6.2.4 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury 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 alkaline phosphatase are outlined in Table 6-4.

Table 6-4. AMG 510 Hepatotoxicity Guidelines

- If the conditions for permanent discontinuation are met (below): Subject to be permanently discontinued
  - AST or ALT > 3 x ULN and INR > 1.5 x ULN (for subjects not on anticoagulation therapy) in the presence of no important alternative causes for elevated AST/ALT values

    OR
  - AST or ALT > 3 x ULN and TBL > 2 x 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 AMG 510 relation to increase in LFTs cannot be excluded, proceed with guidelines below:

CTCAE Grade	AMG 510 Action	Medical Management	Monitoring and Follow-up
Grade 2 AST or ALT and ALP ≤ 8 x 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	Initiate steroids[b]	• Closely monitor liver function tests • Await resolution to baseline or grade 1 and resolution or improvement of hepatitis symptoms • Restart at 1 dose level reduction[c, e]
	Withhold		
	Second Occurrence	Initiate steroids[b]	• Closely monitor liver function tests • Await resolution to baseline or grade 1 and resolution or improvement of hepatitis symptoms • Resume at an additional 1 dose level reduction only with MEDICAL MONITOR approval[c, e]
	Withhold		
	Third Occurrence	NOT APPLICABLE	
	Permanently discontinue AMG 510		

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 AMG 510.

[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 AMG 510.**

[c] Close monitoring at restart (eg, daily LFTs x 2, then weekly x 4). AMG 510 dose may be increased after discussion with medical monitor.

[d] There is no limit to the number of AMG 510 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 preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Subjects who meet eligibility criteria will be assigned to treatment with AMG 510.

6.4.2 Blinding

This is an open-label study that is not blinded.

6.5 Treatment Compliance

A paper diary will be provided to subjects at the beginning of each cycle and the study staff will provide guidance to the subjects on how to complete the diary.

Compliance with treatment and the corresponding assessments should be followed according to the Schedule of Activities (Section 1.3) and the treatment procedures (Section 8.2).

6.6 Treatment of Overdose

Neither the effects of overdose of AMG 510 nor an antidote to overdose are known.

For this study, any dose of AMG 510 greater than 960 mg QD within an 18-hour time period will be considered an overdose.

In the event of an overdose, the investigator/treating physician should:

- **Contact Amgen medical monitor immediately.**
- **Closely monitor the participant for any adverse event/serious adverse event and laboratory abnormalities for at least 7 days.**
- **Document the quantity of the excess dose as well as the duration of the overdose in the Case Report Form (CRF).**

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior therapies that were being taken/used from the original diagnosis through enrollment will be collected. For prior anticancer therapies, collect line of therapy, regimen/agent, type of therapy, setting, start date, stop date, reason for stopping therapy, dose, unit, route, frequency, best response, date of best response, and date of progression documented. For prior radiotherapy for current malignancy, collect body

site, sub site, setting, type, start date, stop date, total dose, unit, best response, was chemotherapy part of concurrent therapy, did documented progression occur in this area, date progression documented. For prior surgeries for current malignancies collect date of surgery, surgery, reason for surgery, body site, subsite, intent of surgery, residual disease.

All other prior therapies that were being taken 28 days before enrollment through enrollment should be collected on each subject's eCRF(s). 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 AMG 510 with **PPI (eg, Omeprazole) or** H2-receptor antagonists **(eg, famotidine) decreased AMG 510 concentrations, which may reduce AMG 510 efficacy. Avoid** use of **PPI or H2-receptor antagonists with AMG 510. If antacid therapy is considered medically necessary, administer AMG 510 4 hours before or 10 hours after administration of a local antacid.**

Breast cancer **resistance protein substrates should** be **used with caution when co-administered with AMG 510 which may increase the circulating concentration of BCRP substrates.**

Amgen will review all concomitant medications with the investigators prior to dosing with AMG 510 to ensure patient safety.

All concomitant therapies (including all prescription, over-the-counter medications) are to be collected from enrollment through the end of the SFU period and will be recorded on the eCRF.

For concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

7. Discontinuation Criteria

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 Sections 7.1, 7.2.1, and 7.2.2.

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 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) and collection of data, including endpoints and adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or 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.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 11.3.

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
- protocol deviation
- non-compliance
- requirement for alternative therapy

- disease progression as defined by RECIST version 1.1 criteria (Section 11.8)
- pregnancy

7.2 Discontinuation 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 to the 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 can 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).

As protocol waivers or exemptions are not allowed 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.

Ongoing patients who are unable or unwilling to attend protocol-specified trial visits and procedures should generally remain on study even if AMG 510 is interrupted, as continued collection of even limited clinical information is valuable for safety and efficacy assessments. In cases where the patient is unable to visit the site, Amgen has explored alternative methods for safety assessments and continuation of study medication (eg, phone contact, virtual visit, alternative location for assessment including local labs or radiological assessment, direct to patient shipment of investigational product where possible). Each case should be discussed with the medical monitor before temporary adjustments are made to the subject's schedule of activities.

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 written consent has been obtained, subjects will be screened in order to assess eligibility for study participation. **Laboratory assessments that were performed as standard of care prior to signing the informed consent may be used for screening assessments if**

they were performed within the allowed 28-day screening window prior to cycle 1 day 1. All screening procedures must be performed within 28 days prior to start of investigational product administration, unless otherwise noted.

Subjects who meet the inclusion and exclusion criteria will be eligible to be enrolled in the study. If a subject has not met all eligibility criteria at the end of the 28-day window, the subject will be registered as a screen failure. Subjects who screen fail may be eligible for re-screening at the investigator's discretion after consultation with Amgen (see also below for details on re-screening).

Laboratory assessments used to determine subject eligibility may be repeated once for confirmation during the 28-day screening period before the subject is considered a screen failure. If laboratory assessments are repeated during the screening period, the result of the last sample taken prior to start of treatment with AMG 510 will be taken into account for determination of subject eligibility.

The following procedures are to be completed during the screening period at the time points designated in the Schedules of Activities (Table 1-1).

Assessments that were performed as standard of care prior to signature of informed consent, but within **the allowed 28**-day **screening window** prior to start of treatment with AMG 510 can be used as screening assessments and do not need to be repeated to confirm subject eligibility.

Rescreening:

Subjects may be rescreened up to 2 times at the discretion of the investigator, after consultation with Amgen. The subject must be reconsented if a rescreening attempt occurs more than 30 days after the original signing of the ICF.

Rescreened subjects must be documented as screen-failed in the subject's medical record and subsequently documented as rescreened. Subjects will retain the same subject identification number assigned at the time of initial screening. Once the subject is recorded as rescreened, a new 28-day screening window will begin. 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 AMG 510.

- Imaging assessments do not need to be repeated if they were performed within 4 weeks prior to start of treatment with AMG 510.
- Central confirmation of *KRAS p.G12C* status (if applicable)

Any other assessments do not need to be repeated if they were performed within **the allowed 28-day screening window** prior to start of treatment with AMG 510.

8.1.2 Treatment Period

Treatment begins on day 1 of cycle 1 when the first dose of investigational product is administered to a subject. AMG 510 will be administered orally QD for 21-day cycles, with no drug holidays between each cycle.

During clinic visit days all protocol-required predose assessments have to be performed prior to administration of AMG 510. Predose is defined as a time before dosing. For laboratory assessments, predose assessments may be performed within ± 1 day for cycle 1 (except cycle 1 day 1 and cycle 1 day 8 where the window is -1 day) and cycle 2 and ± 2 days after cycle 2.

Results of any predose laboratory tests will not have to be available before the administration of AMG 510. Laboratory assessments that were done within 24 hours prior to AMG 510 administration do not need to be repeated.

AMG 510 will be dispensed to subjects at the beginning of each cycle and the subjects are required to bring the bottle of AMG 510 to clinic during clinic visit days. AMG 510 administration should be done in the clinic after all pre-dose assessments have been performed during clinic visit days.

A paper diary will be provided to subjects at the beginning of each cycle and the study staff will provide guidance to the subjects on how to complete the diary.

Administration of AMG 510 may continue until there is evidence of disease progression, intolerance to study medication, or withdrawal of consent.

8.1.3 End of Treatment Visit

For subjects who discontinue investigational product, the end of treatment visit should occur as soon as possible (within 14 days) after the last dose of investigational product.

8.1.4 Safety Follow-up

The SFU visit should occur approximately 30 (+ 7) days after the last dose of AMG 510 or before any new anticancer treatment is started, whichever occurs first. The SFU visit will be the end of study visit for each subject.

8.1.5 End of Study

The end of study visit is defined as last subject last visit (eg, SFU) when assessments and/or procedures are performed.

8.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points. Every effort should be taken to perform assessments on the indicated study day as described in the Schedule of Activities. However, below are the accepted deviation windows for study visits. This should be documented and will not be considered a deviation from the protocol.

- ± 1 day for cycle 1 day 15 and cycle 2 day 8 visits
- ± 2 days for visits during cycle 3 and beyond
- + 7 days for safety follow-up visit

Other general procedure windows:

- Screening assessments: Day -28 to Day 1
- For laboratory assessments, every effort should be taken to perform assessments on the indicated study day. However, a window of ± 1 day is allowable for cycle 1 and cycle 2 (except for cycle 1 day 1 and cycle 1 day 8 where the window is -1 day). A window of ± 2 days is allowable after cycle 2. The same laboratory result should not be used for multiple assessments (for example using cycle 1 day 1 labs for both cycle 1 day 1 and cycle 1 day 2).
- ECGs and vital signs: ± 5 minute window (for time points of 0.25 hour and 0.5 hour postdose), ± 15-minute window for all other postdose time points.
- On days of clinic visits, all predose assessments performed must be completed prior to dose administration (there is no allowance window, only that predose assessments must occur prior to dose administration).
- Pharmacokinetic: blood samples should be collected at the exact nominal time point as noted in the SOA. If it is not possible to collect a blood sample at the specified nominal time point, it should be collected it as close as possible to the nominal time point and the actual collection time recorded. Pharmacokinetic samples not collected at exact nominal time point will not be considered protocol deviations. Predose PK samples should be performed prior to AMG 510 dosing.

8.2.1 General Assessments

8.2.1.1 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.

8.2.1.2 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.

8.2.1.3 Medical History

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

8.2.1.4 Physical Examination

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

8.2.1.5 Physical Measurements

Height (in centimeters) **is only required at screening** and weight (in kilograms) should be measured without shoes.

8.2.1.6 Substance Abuse History

Obtain a detailed history of prior and concurrent use of tobacco.

8.2.1.7 Performance Status

The performance status of each subject will be assessed using the ECOG Performance Status (Section 11.9) and per the time points listed in the Schedule of Activities (Table 1-1).

8.2.2 Efficacy Assessments

Radiological Imaging Assessment

The extent of disease will be evaluated by contrast-enhanced MRI/computed tomography (CT) according to RECIST version 1.1 (Section 11.8). All radiological imaging will be performed as indicated in the Site Imaging Manual provided by the

central imaging core laboratory. In order to reduce radiation exposure for subjects, low-dose CT should be utilized whenever possible.

The screening scans must be performed within 28 days prior to enrollment and will be used as baseline. All subsequent scans will be performed in the same manner as at screening, with the same contrast, preferably on the same scanner. Radiological assessment must include MRI/CT of the chest, abdomen and pelvis, as well as assessment of all other known sites of disease as detailed within the Site Imaging Manual (refer to separate Brain MRI section for details regarding MRI of the brain).

The same imaging modality, MRI field strength and IV and oral contrast agents should be used at screening should be used 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 performed independent of treatment cycle every 6 $\pm$ 1 weeks for the first 4 response assessments, with the first post-baseline scan to occur 6 $\pm$ 1 weeks after cycle 1 day 1. After four 6-week response assessments, radiological imaging and tumor assessment will be performed every 12 $\pm$ 1 weeks. Radiologic imaging and tumor assessment will be performed until disease progression, start of new anticancer treatment, death, withdrawal of consent or until end of study. Imaging may also be performed earlier/more frequently if clinically necessitated at the discretion of the managing physician. Radiographic response (complete response [CR], PR) requires confirmation by a repeat scan at least 4 weeks after the first documentation of response and may be delayed until the next scheduled scan to avoid unnecessary procedures. The minimum time interval for determination of stable disease is $\geq$ 5 weeks.

Radiological imaging assessment during the end of treatment visit should be performed only for subjects that discontinue treatment for a reason other than disease progression per RECIST version 1.1 guidelines.

Determination of disease response for clinical management of subjects will be assessed at the clinical sites per RECIST version 1.1. Scans will be submitted to a central imaging core laboratory for archival, response assessment including RECIST version 1.1, and/or exploratory analysis (eg, volumetric and viable tumor measurements). Detailed

information regarding submission of images to the central imaging core laboratory is found in the Site Imaging Manual.

Brain MRI

All subjects must have MRI of the brain performed within 28 days prior to first dose of AMG 510. Subsequently, brain scans should be performed for all subjects with brain metastases or history of brain metastases and can also be performed at any time if necessary 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.

8.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (see Table 1-1).

8.2.3.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature. The 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 signs eCRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF. Record all measurements on the vital signs eCRF.

8.2.3.2 Electrocardiograms (ECGs)

The subject must be in supine position in a rested and calm state for at least 5 minutes before 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 (all 3 ECGs 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: QRS, QT, QTc, RR, and PR intervals.

- single ECG collected during screening

- 3 baseline ECGs collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (all 3 ECGs should be completed within a total of 5 minutes from the start of the first to the completion of the third) (ie, total ≥ 9 ECGs)
- one triplicate ECG at time points after dosing

Baseline is defined as prior to dosing on cycle 1 day 1. The Principal Investigator or central reader will review all ECGs. Electrocardiograms will be transferred electronically to an ECG central reader 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. In certain circumstances Amgen may be able to provide a standard ECG machine if a site is unable to provide one.

8.2.4 Adverse Events and Serious Adverse Events

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

8.2.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE version 5.0 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 the first dose of investigational product/study treatment through the SFU (end of study) visit are reported using the Event**s** eCRF. All other adverse events possibly related to any study procedures will be reported from the signing of the ICF through the SFU (end of study) visit using the Event**s** eCRF.

8.2.4.1.2 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 ICF through **the safety follow-up visit** or 30 days after the 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.

The criteria for grade 4 in the CTCAE version 5.0 grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

8.2.4.1.3 Serious Adverse Events After the Protocol-required Reporting Period

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 the 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 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.**

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.

8.2.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care should 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.

8.2.4.3 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 Event**s** eCRF.

8.2.4.4 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.

8.2.4.5 Safety Monitoring Plan

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

8.2.4.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and male subjects' female partners will be collected after the start of study treatment and until 7 days after the last dose of AMG 510. Female subjects who become pregnant while on study or within 7 days after receiving the last dose of AMG 510 will not receive subsequent scheduled doses and will be followed for safety until the end of study visit.

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.

8.2.5 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 eCRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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).

Pregnancy Testing

A highly sensitive serum pregnancy test should be completed at screening and a highly sensitive serum or urine pregnancy test should be completed within 7 days of initiation of investigational product and within 7 days of day 1 of each cycle for females of childbearing potential.

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.

Additional serum or urine pregnancy testing should be performed as outlined in the Schedule of Activities (Table 1-1).

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

8.2.6 Pharmacokinetic Assessments

All subjects will have PK samples assessed. AMG 510 must be administered in the fasted state (no food or liquids, except water, 2 hours before to 1 hour after dosing) until cycle 2 day 2 and beyond at which time AMG 510 may be administered with or without food. Subjects will receive AMG 510 with approximately 240 Ml (8 ounces) of water. In the case of vomiting, refer to Table 6-1.

On days in which PK samples are collected, food status will be recorded on each subject's eCRF(s). Subjects will be asked to record the date, time, and number of capsules consumed in a subject drug diary that must be brought to each study visit. The dates of any missed doses or instances of emesis and diarrhea associated with capsule administration will also be recorded in the subject drug diary.

Plasma samples of approximately 3 mL will be collected for measurement of plasma concentrations of AMG 510 at time points as specified in the Schedule of Activities (Table 1-1). A maximum of 3 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.

8.2.7 Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In this study, a specific genomic biomarker (*KRAS p.G12C*) needs to be identified as part of the screening process.

Genomic Biomarker Assessment to Determine Eligibility (*KRAS p.G12C*)

Tumor Tissue

If *KRAS p.G12C* status is not available in the subject's medical record, tumor tissue may be required to identify *KRAS p.G12C* status. Tumor samples may be collected after informed consent is obtained. Tumor tissue may be tested locally or submitted to the central laboratory either as FFPE blocks or unstained slides (see study laboratory manual for details). Tissue should be submitted along with the corresponding pathology report.

If archived FFPE tumor samples are not available, subjects will have the option to undergo a tumor biopsy to identify *KRAS p.G12C* status. When a tumor biopsy is needed to screen for *KRAS p.G12C*, collection of tumor tissue following local standard of

care is not expected to present any additional risk to the health, safety, and welfare of the subject. Screening for *KRAS p.G12C* may be conducted at a central or local laboratory as described in Appendix 2 (Section 11.2).

The tumor block submitted is to be carefully selected by a pathologist or a skilled, experienced histology associate to include generous tumor tissue using the Pathology Report as a guide. In lieu of a block, 20 unstained sections on charged slides from the same block can be submitted.

9. Statistical Considerations

9.1 Statistical Hypotheses

No statistical hypothesis will be tested.

9.2 Sample Size Determination

Up to 18 evaluable subjects will be enrolled in this study. Six DLT-evaluable subjects will be enrolled in cohort 1. If the 960 mg dose (cohort 1) is recommended to be safe and tolerable by the DLRT, up to 6 additional subjects may be enrolled in cohort 1 to gather additional safety, PK, and preliminary efficacy data (up to 12 subjects total enrolled in the study) at the 960 mg dose. Alternatively, if the DLRT recommends to open cohort 2 (720 mg dose), 6 DLT-evaluable subjects will be enrolled in cohort 2. If the DLRT then makes the recommendation to continue cohort 2 at 720 mg, up to 6 additional subjects (up to 18 subjects total enrolled in the study) may be enrolled in cohort 2 to gather additional PK, safety, and preliminary efficacy at the 720 mg dose.

The sample size of 6-DLT evaluable subjects in the dose exploration phase for DLRM is based on practical considerations and is consistent with conventional oncology studies. With 6-DLT evaluable subjects, there is a 47% to 91% probability of observing at least 1 DLT if the true DLT rate is 10% to 33%.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

9.3.1.1 Safety Analysis Set

The safety analysis set will consist of all subjects that are enrolled and receive at least 1 dose of AMG 510.

The analysis of all endpoints, unless noted otherwise, will be conducted on the safety analysis set.

The analysis of DLT will be restricted to DLT-evaluable subjects, which consists of subjects if either: 1) the subject experiences a DLT, or 2) the subject does not

experience a DLT and 3) subject received at least 80% of the planned doses of investigational product within the 21-day DLT window.

9.3.1.2 Pharmacokinetic Analysis Set

The PK Analysis Set will contain all subjects who have received at least 1 dose of AMG 510 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.

9.3.2 Covariates

There are no planned covariates for this study.

9.3.3 Subgroups

Potential subgroups may be pre-specified in the statistical analysis plan.

9.3.4 Handling of Missing and Incomplete Data

Descriptive statistics will be used to identify the extent of missing data. Missing or incomplete dates that are critical for the analysis (eg, date of death, adverse event start date) will be imputed. Detailed imputation rules will be documented 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 4.4.1.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

9.4.1.1.1 Cohort 1 (Dose Exploration – first 6 DLT-evaluable subjects in cohort)

Safety data will be reviewed on an ongoing basis. The first DLRM will occur after the first 6 DLT-evaluable subjects enrolled in cohort 1 have the opportunity to receive 21 days treatment. In the dose level review meetings, Amgen, in consultation with the site investigators, will review all available cumulative data by cohort prior to making dose determination recommendations. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all dose level review meetings and considered in all enrollment and dosing recommendations. Additional details regarding the dose review meeting are providing in Section 11.3.

The DLRT will be composed of the investigators, Amgen Medical Monitor, Amgen Global Safety Officer (GSO), Amgen Early Clinical Development Manager, and Biostatistics representative. Additional members may be added as needed (eg, PK Scientist). A quorum, defined as the majority of actively screening and enrolling investigators or their qualified designee (ie, sub-investigator possessing hard copy documentation [eg, email] of the investigator's recommendation regarding the dose level review), must be in attendance for DLRM to proceed. The DLRM will be rescheduled if a quorum is not reached. Voting members of the DLRM will include the Amgen Medical Monitor, the Amgen GSO, and all actively screening and enrolling investigators or their qualified sub-investigator designee.

The team may recommend de-escalation to a lower dose, or termination of the study. The Amgen Medical Monitor and GSO and the majority of actively screening and enrolling investigators participating in the DLRM must cast a positive vote indicating an acceptable safety profile was observed for AMG 510 to allow the dose level modification and/or cohort continuation/expansion to proceed. Available study data including demographics, smoking status (prior and current), medical history, concomitant medications, **adverse events**, ECGs, vital signs, laboratory results, emerging PK or pharmacodynamics, and emerging efficacy data will be reviewed.

The following recommendations will be made by the DLRT:

- dose de-escalation recommendations
- number of subjects per cohort
- continuation, delay or termination of dosing
- change of the dosing schedule
- termination of the study

9.4.1.1.2 Cohort 2 (Dose Exploration – first 6 DLT-evaluable subjects in cohort)

If in cohort 1, DLRT makes the recommendation to open cohort 2 (720 mg), the second dose level review meeting will occur after the sixth subject enrolled in cohort 2 has had the opportunity to receive 21 days of treatment.

The same DLRT will be responsible for reviewing all cumulative available data by cohort. The same procedure and principal described in cohort 1 dose level review meeting will be applied in cohort 2 as well.

9.4.1.2 Primary Analysis

The primary analysis will occur after all subjects (6 to 12 subjects) enrolled in cohort 1 and after all 6 to 12 subjects enrolled in cohort 2 (if ≥ 2 DLTs are observed in the first 6 subjects in cohort 1) have had the opportunity to complete 6 months on study or have been withdrawn from study.

9.4.1.3 Final Analysis

A final analysis is planned after all cohorts have ended the study. Primary and final analysis may be combined in case all subjects have ended study close to the time point of the primary analysis.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, and preliminary efficacy data by dose, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Subject listings for time-to-event endpoints may be provided instead of Kaplan-Meier estimates or Clopper Pearson exact confidence interval if the analysis set has fewer than 10 subjects. Graphical summaries of the data may also be presented.

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable to the study
Secondary	Listings of secondary efficacy endpoints will be produced for all subjects. The proportion of subjects with an objective response, defined as CR + PR (assessed per RECIST version 1.1) will be described. Similarly for proportion of subjects with disease control, defined as CR + PR + SD will be described. For all subjects treated at the planned dose, the Kaplan-Meier method will be used for time-to-event endpoints to estimate the survival curve, quartiles, and rates at selected timepoints with 95% CI for 1) duration of response, 2) progression-free survival, and 3) duration of stable disease. Event-free rates at 3-month intervals will be estimated using the Kaplan-Meier method for progression-free survival (PFS). Time to response will be summarized by the nonmissing sample size (n), standard deviation, median, minimum, and maximum for responders. For secondary endpoint definitions, refer to the statistical analysis plan.

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the safety analysis set, which includes subjects that are enrolled and received AMG 510. The statistical analysis methods are described in Section 9.4.2.3.2 through Section 9.4.2.3.5.

9.4.2.3.2 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, adverse events leading to withdrawal from investigational product, and adverse events of interest (if applicable) will also be provided.

9.4.2.3.3 Laboratory Test Results

Summaries of laboratory data over time and/or changes from baseline over time will be provided. Tables of maximum shifts from baseline to the worst on-study value will be provided for selected laboratory values with National Cancer Institute-CTCAE grades.

9.4.2.3.4 Vital Signs

Summaries of vital signs data over time and/or changes from baseline over time will be provided.

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 QTcF will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized.

All on-study ECG data will be listed.

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 AMG 510.

Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given.

9.4.2.3.7 Exposure to Concomitant Medication

Number and proportion of subjects receiving concomitant medication will be summarized by preferred term as coded by the World Health Organization Drug Dictionary.

9.4.2.4 Other Analyses

For AMG 510, PK parameters including, but not limited to C_{max}, t_{max}, and AUC will be determined from the concentration-time profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. Based on the review of the data, analyses to describe the relationship between AMG 510 exposure and either pharmacodynamic effect and/or clinical outcome may also be performed.

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
BCRP	**breast cancer resistance protein**
CFR	U.S. Code of Federal Regulations
C_{max}	maximum observed plasma concentration
COVID-19	**coronavirus disease 2019**
CR	complete response
CRC	colorectal cancer
CRF	**Case Report Form**
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interactions
DES	Amgen data element standard
DILI	drug induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
EMR	**Electronic Medical Record**
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early

Abbreviation or Term	Definition/Explanation
End of Study (end of trial)	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), following any additional parts in the study, as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
ERK	extracellular signal-regulated kinase
FDA	**Food and Drug Administration**
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GDP	guanosine diphosphate
GI	gastrointestinal
GLP	Good Laboratory Practice
GSO	Global Safety Officer
GTP	guanosine triphosphate
Hep	hepatitis
HepBsAg	hepatitis B surface antigen
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
HRT	hormonal replacement therapy
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	**interstitial lung disease**
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IV	intravenous
KRAS	Kirsten rat sarcoma
MATE1	multidrug and toxin extrusion protein 1
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high

Abbreviation or Term	Definition/Explanation
NCT	National Clinical Trials
NE	not evaluable
NSCLC	non-small cell lung cancer
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PO	administered orally
PPI	**proton pump inhibitor**
PR	partial response
Q2C	every other cycle from cycle 7 and beyond
QC	every cycle from cycle 7 and beyond
QD	once daily
QTc	corrected QT interval
RAF	rapidly accelerated fibrosarcoma
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
rSDR/V	**remote Source Data Review and Verification**
Screen	screening
SD	stable disease
SFU	safety follow-up
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOS1	son-of-sevenless homolog 1
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
STD_{10}	severely toxic dose in 10%
Study day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin

Abbreviation or Term	Definition/Explanation
$t_{1/2,z}$	terminal half-life associated with λ_z
t_{max}	time to achieve C_{max}
ULN	upper limit of normal
VEGF	**vascular endothelial growth factor**
WBC	white blood cell

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.

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: Chemistry	Local Laboratory: Coagulation	Local Laboratory: Urinalysis	Local Laboratory: Hematology	Central Laboratory
sodium potassium chloride bicarbonate total protein albumin calcium magnesium phosphorus glucose BUN or urea creatinine total creatine kinase total bilirubin direct bilirubin ALP AST (SGOT) ALT (SGPT) Glomerular filtration rate (derived)	PT/INR PTT/aPTT fibrinogen **(optional)** D-dimer **(optional)** **Local Laboratory: Serology** Hep B surface antigen Hep C antibody Anti-HBs **Local Laboratory: Thyroid Panel** TSH Total T3 (or free T3 per local standard) Free T4 **Local Laboratory: Lipid Panel** total cholesterol LDL	specific gravity pH blood protein glucose bilirubin ketones sodium **(optional)** potassium **(optional)** **M**icroscopic exam[c]: • cellular casts • granular casts • hemoglobin casts • hyaline casts • mixed casts • WBC • RBC • epithelial cells • bacteria • urine casts	RBC hemoglobin hematocrit MCV platelets calculated absolute neutrophil count (derived) WBC differential: • total neutrophils • eosinophils • basophils • lymphocytes • monocytes	PK sampling tumor biopsy[b]

Local Laboratory: Chemistry	Local Laboratory: Coagulation	Local Laboratory: Urinalysis	Local Laboratory: Hematology	Central Laboratory
	HDL triglycerides			
	Local Laboratory: Other			
	HbA1c Serum or urine pregnancy[a]			

Footnotes defined on next page
ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; INR = international normalized ratio; LDL = low density lipoprotein; MCV = mean corpuscular volume; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell count.
Note: For creatinine clearance calculation, Modification of Diet in Renal Disease formula should be used: GFR (mL/min/1.73 m^2) = 175 x SCr (mg/dL)$^{-1.154}$ x age$^{-0.203}$ x 0.742 (if female) x 1.21 (if African American) x 0.763 (if Japanese) x 1.233 (if Chinese).
[a] For female subjects of childbearing potential only. At screening, a highly sensitive serum pregnancy test is required. For all other time points, a highly sensitive serum or urine pregnancy test is required.
[b] Only applicable if *KRAS p.G12C* status is unknown at screening. Archived FFPE tumor tissue is acceptable. If archived tumor tissue is not available, a tumor biopsy may be performed. Testing for *KRAS p.G12C* can be performed locally or centrally.
[c] **Microscopic exam to be performed at the discretion of the investigator.**

11.3 Appendix 3. Study Governance Considerations

Dose Level Review Meetings (DLRM)

A DLRM is conducted to review and interpret safety data for the purposes of making recommendations dose level de-escalation, cohort continuation, or cohort expansion; making recommendations about non-dose escalation cohorts (eg, expanded, highest dose and/or final cohort); and evaluating safety signals for purposes of applying Dose Cohort Stopping Rules. The required Dose Level Review Team (DLRT) members are the Medical Monitor, Global Safety Officer (GSO), and site investigators. The DLRT will include all site investigators. The Medical Monitor, GSO, and site investigators are the only voting DLRT members. Additional members may be added as needed (eg, Pharmacokinetics [PK] Scientist).

The Medical Monitor must be in attendance and cannot be represented by a voting designee or delegate. Voting designees can be identified as appropriate by the GSO or site investigator(s). A site investigator may identify a delegate (eg, sub-investigator) who is listed in the Delegation of Authority. If a site investigator does this, the site investigator must provide written agreement with the designee or delegate's vote.

For a DLRM to occur, the Medical Monitor must attend, and the GSO or delegate must attend. In addition, a quorum of site investigators must be present. A quorum is defined as the majority of actively screening and enrolling investigators or their qualified designees (ie, sub-investigator possessing hard copy documentation [eg, email] of the investigator's recommendation regarding the dose level review). The DLRM will be rescheduled if these requirements are not met.

Available study data, including demographics, smoking status (prior and current), medical history, concomitant medications, adverse events, electrocardiograms (ECGs), vital signs, laboratory results, emerging PK or pharmacodynamics, and emerging efficacy data will be reviewed.

Dose Level Review Meeting voting will occur as follows: there will be a total of 3 votes, 1 for the Medical Monitor, 1 for the GSO or delegate, and 1 for all of the site investigators or delegates combined. Regardless of how many site investigators there are, all of the site investigators combined will have a total of 1 vote decided by a majority of the investigators (defined as greater than or equal to 50%).

DLRM recommendations to escalate to the next planned cohort (if applicable), must be by unanimous vote. If the voting members of the DLRT are not able to reach a

unanimous recommendation on whether to escalate to the next planned cohort or to an intermediate cohort, then this should be reflected in the DLRM Memo (FORM-115760). Other recommendations, such as expanding a cohort or lowering a dose will be made by a majority vote.

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 Conference on 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 at any time. 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. 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.

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 ICF(s) 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 30 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.

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.

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.

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 national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those patients who participate in the trial and who did not object to remote access to their medical records. A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorized access, access rights should be revoked once rSDR/V tasks have been completed for the trial. The EMR system should have an audit trail and be able to log information on who accessed data and when. Remote access to the EMR should only be possible using a two-factor authentication.

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.

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

Case report forms 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 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).

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 prestudy 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

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

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 an extension 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 statistical analysis plan.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an adverse event or serious adverse event is due to advanced/metastatic solid tumors, 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 CRF.
- The investigator must assign the following adverse event attributes:
  - adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - dates of onset and resolution (if resolved);
  - Did the event start prior to first dose of investigational product;
  - assessment of seriousness;
  - severity (or toxicity defined below);
  - assessment of relatedness to investigational product (AMG 510), other protocol-required therapies, and/or study-mandated **activity and/or** procedures and;
  - 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 highest grade on the Events electronic CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the 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, protocol-required therapies, and/or study-mandated **activity and/or** procedure and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by 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 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 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

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

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Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN Study # 20190147 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 eeath. 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 (AMG 510)** or an Amgen device used to administer the IP?			**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						AMG 510				
						No✓	Yes✓			
				☐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

		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 #**
IP/Amgen Device:								
AMG 510	☒ **open label**							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN
Study # 20190147
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											
	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 # 20190147 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	Title	Date
_____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*		

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

Study-specific contraception requirements for male and female subjects 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 must receive pregnancy prevention counseling and be advised of the 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 AMG 510.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and/or for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

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

Note: Failure rate of < 1% per year when used consistently and correctly.

- 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 an acceptable method of effective contraception such as: hormonal, intrauterine device, intrauterine hormonal-releasing system, female barrier method (diaphragm, cap, sponge [a female condom is not an option 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.

Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- periodic abstinence (calendar, symptothermal, post-ovulation methods)
- withdrawal (coitus interruptus)
- spermicides only
- lactational amenorrhea method

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 an additional 7 days after the last dose of AMG 510.

- 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 authorization 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 the end of study visit. 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) 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 (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant

- 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).
- 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 an additional 7 days after the last dose of AMG 510.
- Information will be recorded on the Lactation Notification Form (see Figure 11-2 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 215.
- 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 the end of study visit after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms

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: 20190147

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
AMG 510				mm_____/dd_____/yyyy_____

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

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: 20190147

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
AMG 510				mm_____/dd_____/yyyy_____

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

11.6 Appendix 6. Sample Storage and Destruction

Any blood or tissue samples 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, Amgen can perform additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the solid tumors, the dose response and/or prediction of response to AMG 510, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic or other exploratory studies 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 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

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

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

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

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

- hepatobiliary tract disease
- viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- alpha-one antitrypsin deficiency
- alcoholic hepatitis
- autoimmune hepatitis
- Wilson's disease and hemochromatosis
- nonalcoholic fatty liver disease including steatohepatitis
- non-hepatic causes (eg, rhabdomyolysis, hemolysis)

If investigational product(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 11-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3 x ULN at any time	> 2 x ULN
		OR
INR	--	> 1.5 x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 5 x ULN at any time	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values
	> 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	> 3 x ULN (when baseline was < ULN)
	OR	
ALP	> 8 x 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 11-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Event 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 11-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (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 v1.1)

Quick Reference

Definitions

- Measurable Lesions
  - Measurable 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/magnetic resonance imaging (CT/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.
  - Nodal Lesions - Lymph nodes are to be considered pathologically enlarged and measurable, a lymph node must be ≥ 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.
    - Nodal size is normally reported as 2 dimensions in the axial plane. The smaller of these measures is the short axis (perpendicular to the longest axis).
  - 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 in the lesion prior to enrollment.
- Non-measurable Lesions
  - All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm but to < 15 mm short axis with CT scan slice thickness no greater than 5 mm) are considered non-measurable and characterized as non-target lesions.
  - Other examples of non-measurable lesions 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.
    - Biopsied lesions
    - Categorially, clusters of small lesions, bone lesions, inflammatory breast disease, and leptomeningeal disease are non-measurable.

Methods of Measurement

- Measurement of Lesions - The longest diameter of selected lesions should be measured in the plane in which the images were acquired (axial plane). All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 4 weeks before study Day 1.
- Methods of Assessment - The same method of assessment and the same technique should be used to characterize each identified and reported lesion throughout the trial.
- 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 ≤ 5 mm thick contiguous slices.

Baseline documentation of "Target" and "Non-target" lesions

- 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.
  - Pathologic lymph nodes (with short axis ≥ 15 mm) may be identified as target lesions. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-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.
- Non-Target Lesions - All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, and these lesions should be followed as "present", "absent", or "unequivocal progression" throughout the study. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
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 relative 20% increase and an absolute increase of 5 mm in the sum of the diameters of target lesions, taking as reference the smallest sum on study, or the appearance of 1 or more new lesions.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters since the treatment started.

Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Incomplete Response/Stable Disease (SD)	Persistence of one or more non-target lesions(s) and/or maintenance of I' level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions and/or appearance of one or more new lesions[a].

[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.

Evaluation of Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment or disease progression/recurrence (taking as reference for progressive disease [PD] the smallest measurements recorded since the treatment started).

In general, 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.

Time Point response: Subjects with Target (± Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

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

Time Point Response: Subjects with Non-target Disease Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease.

[a] "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.

Overall Response: 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, 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.

Special Notes on Response Assessment

- Nodal lesions – Lymph nodes identified as target lesions should always have the actual short axis measurement recorded, even if the nodes regress to below 10 mm on study. In order to qualify for complete response (CR), each node must achieve a short axis < 10 mm, NOT total disappearance. Nodal target lesion short axis measurements are added together with target lesion' longest diameter measurements to create the sum of target lesion diameters for a particular assessment (timepoint).
- 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. If a lesion becomes less than 5 mm, the accuracy of the measurement becomes reduced. Therefore, lesions less than 5 mm are considered as being "too small to measure" and are not measured. With this designation, they are assigned a default measurement of 5mm. No lesion measurement less than 5 mm should be recorded, unless a lesion totally disappears and "0" can be recorded for the measurement.
- New lesions – The term "new lesion" always refers to the presence of a new finding that is definitely tumor. New findings that only may be 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 repeat scans confirm 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.
- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression with an additional imaging assessment 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 fluorodeoxyglucose-positron emission tomography (FDG-PET) or PET/CT, or possibly fine needle aspirate/biopsy, to confirm the CR status.

Confirmation Measurement / Duration of Response

- **Response Confirmation -** In non-randomized trials where response is the primary endpoint, confirmation of PR and CR at least 4 weeks after the initial assessment is required to ensure responses identified are not the result of measurement error.
- **Duration of overall response** – The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date the recurrent or PD is objectively documented.
- **Duration of Stable Disease -** SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.9 Appendix 9. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status

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 selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 – Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 – Completely disabled. Cannot carry out any selfcare. Totally confined to bed or chair

5 – Dead

11.10 Appendix 10. Examples of Excluded Treatments

Examples of sensitive clinical substrates for CYP3A-mediated metabolism
alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil
Examples of strong clinical inhibitors for CYP3A-mediated metabolisms
boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole
Examples of strong clinical inducers for CYP3A-mediated metabolisms
carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Amendment 4

Protocol Title: A Phase 1, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 in Subjects of Chinese Descent With Advanced/Metastatic Solid Tumors With *KRAS p.G12C* Mutation (CodeBreaK 105)

Amgen Protocol Number AMG 510 20190147

Amendment Date: 05 January 2022

Rationale:

This protocol has been amended mainly to:

- Update dosage modification guidelines for hematologic and non-hematologic toxicities (Section 6.2.3.1, Table 6-3) and dosing instructions for AMG 510 (Section 6.1.1, Table 6-1) as the Amgen investigational product in the study.
- Update key safety information to be monitored in the clinical study, newly added information pertaining to thyroid abnormalities, and interstitial lung disease/pneumonitis (Section 2.3).
- Clarify definition of AMG 510 overdose and instructions for the physician/investigator to manage such event (Section 6.6).
- Add information regarding the treatments that must be avoided prior to enrollment and during the study period (Sections 6.1.7 and 6.7.2) and instructions on how to administer such medications (concomitant medications) in case they are considered a medical necessity (ie, antacid therapy).
- Update instructions for reporting serious adverse events observed by the investigator or reported by the subject during the study and after end of study (Sections 1.3 and 8.2.4) as well as language related to definitions and procedures for recording, evaluating, follow-up and reporting safety events (Section 11.4).

- Clarify that standard of care treatment (eg, procedures, laboratory studies) can be used during the screening process if they were conducted within the 28-day screening window prior to cycle 1 day 1 (Sections 1.1, 5, 8.1.1).
- Clarify nature of laboratory assessments in the schedule of activities (ie, lipid panel) and inform that local urinalysis and coagulation assessments are at the discretion of the investigator (Section 1.3, 11.2).
- Add background information regarding AMG 510 as a new approved treatment for adult patients with *KRAS pG12C*-mutated locally advanced or metastatic non-small cell lung cancer (Section 2.2.1).
- Clarify that individuals who experience a screen failure may be rescreened up to 2 times (Section 5.3).
- Update study assessments and procedures to describe alternative methods to continue safety assessments and study medication in patients unable to visit the study sites (Section 8) and to describe requirement for completion of physical measurements (Sections 1.3 and 8.2.1.5).
- Add language pertaining to Coronavirus disease 2019 (COVID-19) related benefit/risk assessment (Section 2.3).
- Add strategies to increase data quality assurance including implementation of the remote Source Data Review and Verification and read-only access for the clinical monitor to the electronic medical record system (Section 11.3).
- Provide general clarifications about the use of investigational medical devices in this study (Section 6.1.3) and about product complaints (Section 6.1.6).
- Multiple changes for clarification, administrative, typographical, and formatting were made throughout the protocol.

Amendment 3

Protocol Title: A Phase 1, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 in Subjects of Chinese Descent With Advanced/Metastatic Solid Tumors With *KRAS p.G12C* Mutation (CodeBreaK 105)

Amgen Protocol Number AMG 510 20190147

Amendment Date: 16 December 2020

Rationale:

This protocol is being amended to:

- To add additional subjects at a dose level considered safe and tolerable by the dose level review team (DLRT) to collect additional pharmacokinetic (PK), safety, and preliminary efficacy data.
- To clarify allowable time windows for visits and study-required assessments.
- To add additional concomitant medication use information regarding gastric acid controllers based on developing pharmacokinetic data.
- Updates to statistical sections to align with the addition of more subjects to the study.
- Corrections and clarifications to the analyte Table 11-1.

Amendment 2

Protocol Title: A Phase 1, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 in Subjects of Chinese Descent With Advanced/Metastatic Solid Tumors With KRAS p.G12C Mutation (CodeBreaK 105)

Amgen Protocol Number AMG 510 20190147

Amendment Date: 18 September 2020

Rationale:

This amendment is being updated to:

- Remove the timing requirement for predose safety lab assessments
- Changes to eligibility to have received an anti-PD(L)1 and/or platinum as well as received 2 prior systemic therapies rather than 3
- Clarification of a second DLRM for the second cohort
- Remove thyroid panel assessment at cycle 1 day 1
- Added key safety information (increases in AST and ALT)
- Other administrative changes (typographical, formatting)

Amendment 1.0

Protocol Title: A Phase 1, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 in Subjects of Chinese Descent With Advanced/Metastatic Solid Tumors with *KRAS p.G12C* Mutation (CodeBreak 105)

Amgen Protocol Number: AMG 510 20190147

Amendment Date: 04 February 2020

Rationale:

The below AMG 510 program-wide changes were incorporated into the study:

- Thyroid function, cholesterol, and triglyceride tests were added to the Schedule of Activities in this study to make it consistent with Study 20170543 that was amended to address regulatory agency feedback (US Food & Drug Administration)
- Removed food restriction for AMG 510 at cycle 2 day 2 and beyond (after intensive pharmacokinetics assessments) as the studies evaluating the effect of food (high fat meal) on pharmacokinetic characteristics of AMG 510 demonstrated that high-fat meal does not appear to result in clinically meaningful alteration of AMG 510 exposure
- Removed reference to “30 tablets/bottle” to allow flexibility in AMG 510 supply
- Updated language for AMG 510 dose modification to allow additional dose reductions of AMG 510 in the case of indicated toxicities
- Added AMG 510 Hepatotoxicity Guidelines for management and monitoring of subjects with increased AST, ALT, or ALP while on trial
- Revised the Contraceptive Guidance and Collection of Pregnancy and Lactation Information based on data from recently completed nonclinical studies (absence of genotoxic risk for AMG 510 based on recently completed GLP-compliant in vitro bacterial mutagenicity Ames assay and in vivo genotoxicity study including the erythrocyte micronucleus test and the alkaline comet assay).
- Modified hepatotoxicity stopping rules (Appendix 7) to align with guidelines for the management of AMG 510 hepatotoxicity

Other Changes:

- Added CodeBreak 105 study name
- Removed exploratory objective/endpoint to identify metabolites of AMG 510 in plasma and urine
- Modified header rows in Schedule of Activities to clarify that assessments on cycle 2 day 8, cycles 3,5;4,6; QC and Q2C will be completed prior to dosing
- Clarified timepoints for electrocardiogram and vital signs assessments in Schedule of Assessments footnote e

- Changed language to allow MRI brain scans to be performed in all subjects at screening, and in subjects with brain metastases or history of brain metastases at other indicated timepoints
- Added language to update AMG 510 nonclinical toxicology information with 3-month dog and rat results.
- Added language to clarify the definition of predose and timepoint window for predose laboratory assessments
- Added language to clarify the minimum time interval for determination of stable disease
- Modified table of analyte listings in Appendix 2 to include new laboratory tests
- Corrected the number of target lesions for RECIST v1.1 in Appendix 8
- Added language to clarify that an assessment of PR and CR must be confirmed ≥ 4 weeks after the initial assessment
- Added a new appendix to present examples of excluded treatments
- Administrative and editorial updates