Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Hong DS, Fakih MG, Strickler JH, et al. $KRAS^{G12C}$ inhibition with sotorasib in advanced solid tumors. N Engl J Med 2020;383:1207-17. DOI: 10.1056/NEJMoa1917239

This supplement contains the following items:

1. Original protocol
2. Current protocol
3. Summary of protocol amendments
4. Original statistical analysis plan
5. Current statistical analysis plan
6. Summary of statistical analysis plan amendment

Title: A Phase 1, First-in-Human, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 in Subjects With Advanced Solid Tumors With a Specific KRAS Mutation

Amgen Protocol Number (AMG 510) 20170543

EudraCT number 2018-001400-11

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Date: 14 May 2018

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I have read the attached protocol entitled "A Phase 1 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 in Subjects With Advanced Solid Tumors with a Specific KRAS Mutation", dated 14 May 2018, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) 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)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one 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)

Protocol Synopsis

Title: A Phase 1, First in Human, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy, of AMG 510 in Subjects with Advanced Solid Tumors with a Specific KRAS Mutation

Study Phase: 1

Indication: Advanced *KRAS p.G12C* mutant solid tumors

Primary Objective:

- Evaluate the safety and tolerability of AMG 510 in adult subjects with *KRAS p.G12C* mutant solid tumors
- Estimate the maximum tolerated dose (MTD) and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) within investigated subject population groups

Secondary Objectives:

- Characterize the pharmacokinetics (PK) of AMG 510 following administration as an oral tablet formulation
- To evaluate tumor response assessed by CT or MRI using RECIST 1.1 criteria of AMG 510 as monotherapy in subsets of solid tumors with *KRAS p.G12C* mutation
- To evaluate the effect of food on the oral pharmacokinetics of AMG 510
- To evaluate the relationship between changes in QTc and AMG 510 exposure

Exploratory Objectives:

- To explore pharmacokinetic/pharmacodynamic relationships for safety and/or efficacy endpoints
- To characterize AMG 510 excretion in urine
- To identify metabolites of AMG 510 in plasma and urine
- To investigate potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor samples.

Hypothesis:

At least 1 dose level of AMG 510, in repeat oral administrations, will achieve acceptable safety and tolerability in subjects with advanced *KRAS p.G12C* mutant solid tumors, with evidence of anti-tumor activity

Primary Endpoints:

- Safety: subject incidence of dose limiting toxicity (DLTs), treatment-emergent adverse events, treatment-related adverse events, and clinically significant changes in vital signs, physical examinations, electrocardiogram (ECGs), and clinical laboratory tests

Secondary Endpoints:

- 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)
- Objective response rate (ORR), duration of overall response (DOR), progression-free survival (PFS), and duration of stable disease measured by CT or MRI and assessed per RECIST 1.1 criteria

- PK parameters of AMG 510 including, but not limited to, C_{max}, t_{max}, and AUC in the fed and fasted states for the food effect assessment
- AMG 510 exposure/QTc interval relationship

Exploratory Endpoints:

- AMG 510 exposure/safety and exposure/efficacy relationships
- AMG 510 excretion in urine
- Characterization of potential metabolites of AMG 510 in plasma and urine, if appropriate
- Quantification of biomarker expression at protein, RNA, and DNA levels, as appropriate
- Potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor samples

Study Design: This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study to evaluate safety and tolerability of AMG 510 in subjects with advanced *KRAS p.G12C* mutant solid tumors. The study will be conducted at approximately 25 sites in Australia, United States, Canada, Brazil, France, Germany, China, Japan, and South Korea. Other countries or regions may participate. AMG 510 will be evaluated as an oral therapeutic. The study will be conducted in 2 parts: Part 1 – Dose Exploration and Part 2 – Dose Expansion. Part 1 is aimed at evaluating the safety, tolerability, PK and pharmacodynamics of AMG 510 and determining the MTD of repeat daily (QD) dosing schedule in subjects with advanced *KRAS p.G12C* mutant solid tumors using a Bayesian Logistics Regression Model (BLRM) design. The dose expansion part of the study (Part 2) can open once the MTD and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) has been determined in Part 1. The dose exploration part of the study will consist of approximately 50 subjects and the dose expansion part will consist of approximately 60 additional subjects, including at least 3 groups with specific tumors harboring *KRAS p.G12C* mutations (non-small cell lung cancer [NSCLC], colorectal cancer [CRC], and all other solid tumors). Different schedules can be used in the dose expansion part based on clinical and PK data from all parts of the dose exploration. The DLT evaluation period will be 21 days. Based on emerging clinical efficacy data, the groups explored in the expansion part can be modified. Administration of AMG 510 (in part 1 and part 2) may continue until evidence of disease progression, intolerance to study medication, or withdrawal of consent.

Dose Exploration – Part 1

Dose exploration cohorts will estimate the safety, tolerability, PK, and pharmacodynamics of different doses of AMG 510 in subjects with advanced *KRAS p.G12C* mutant solid tumors. Subjects will receive AMG 510 daily administered orally. Enrollment into the dose exploration cohorts may be from any eligible solid tumor type. Dose escalation will begin with 2-4 subjects treated at the lowest planned dose level of 180 mg. Dose escalation will follow the planned Study Schema schedule with 2-4 subjects treated in each cohort. If no DLT is observed, dose escalation will continue to the next planned dose cohort as per Study Schema. Once a subject experiences a DLT, dosing for subsequent cohorts will be recommended using the dose level recommendation from the Bayesian Logistic Regression Model (BLRM). The decision to advance to the next dose level will be recommended by the Dose Level Review Team (DLRT) using the dose level recommendation from BLRM, as appropriate, and by evaluating available safety data, laboratory, and PK information.

Intra-subject dose escalations are allowed on this study. Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle once the next dose cohort has been deemed safe by the DLRT and after consultation with the sponsor if:

- no DLT has been reported for this subject during or after completion of the DLT period
- the subject has not experienced any ≥ grade 2 adverse events (deemed treatment related by the investigator) during treatment

Subjects who do not proceed to a higher dose may receive extra cycles at the original dose.

Dose exploration will continue until any of the following events.

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 DLT-evaluable subjects)
- The MTD is identified, BLRM recommends a dose level which already has 6 DLT-evaluable subjects

Additional subjects (up to 20) may be enrolled in one or more dose levels that have been shown to be safe and tolerable, defined as backfill enrollment. This backfill enrollment will be done to better estimate the RP2D and better characterize the safety, efficacy and pharmacodynamics for AMG 510 and may be concurrent with dose escalation to identify the MTD. Additionally, food effect evaluation will be conducted in at least 6 subjects from backfill enrollment in cycle 2 or later.

Dose Expansion – Part 2

Upon completing the dose exploration part of the study and depending on data obtained, dose expansion may proceed with three groups consisting of subjects with *KRAS p.G12C* mutant solid tumors:

1. Group 1 (NSCLC) - subjects with advanced *KRAS p.G12C* mutant NSCLC
2. Group 2 (CRC) - subjects with advanced *KRAS p.G12C* mutant CRC
3. Group 3 (Other) - subjects with advanced *KRAS p.G12C* mutant solid tumor types other than the tumor types specified in Groups 1 and 2

Dose expansion in all three groups may be done concurrently.

Sample Size:

Part 1 – Dose Exploration: No more than 50 subjects will be enrolled to the dose escalation cohorts. Approximately 30 subjects will be needed to estimate the MTD. An additional 20 subjects may be enrolled by backfill enrollment from which at least 6 subjects will be evaluated for food effect.

Part 2 – Dose Expansion: Approximately 60 subjects will be enrolled in the dose expansion part of the study, which will be conducted in at least 3 groups. Group 1: up to 20 subjects with advanced KRAS G12C mutant NSCLC. Group 2: up to 20 subjects with advanced KRAS G12C mutant CRC. Group 3: up to 20 subjects with advanced KRAS G12C mutant solid tumor types other than specified in Groups 1 and 2. The sample sizes for groups 1 through 3 are based on practical considerations.

Summary of Subject Eligibility Criteria: Adult subjects (≥ 18 years old) with advanced solid tumors will be eligible for this study. Enrollment will be restricted to subjects with *KRAS p.G12C* mutant solid tumors as assessed by DNA sequencing of tumor biopsy specimens. Once consented to the study, subjects will provide a medical history and undergo screening safety tests to confirm all eligibility requirements of the study have been met. Subjects will provide archived tumor samples (fresh frozen sample or formalin fixed paraffin embedded [FFPE] sample collected within 5 years) or undergo a pre-dose tumor biopsy that enables KRAS testing.

Investigational Product

Amgen Investigational Product Dosage and Administration:

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

Procedures: After written informed consent has been obtained, all screening tests and procedures will be performed within 21 days of administration of the first dose of AMG 510

(day 1), unless otherwise noted. Subjects will be seen in clinic where critical clinical safety and study evaluations will be performed including physical examination, vital signs, clinical laboratory tests, electrocardiograms (ECGs), PK, and biomarker sample collections.

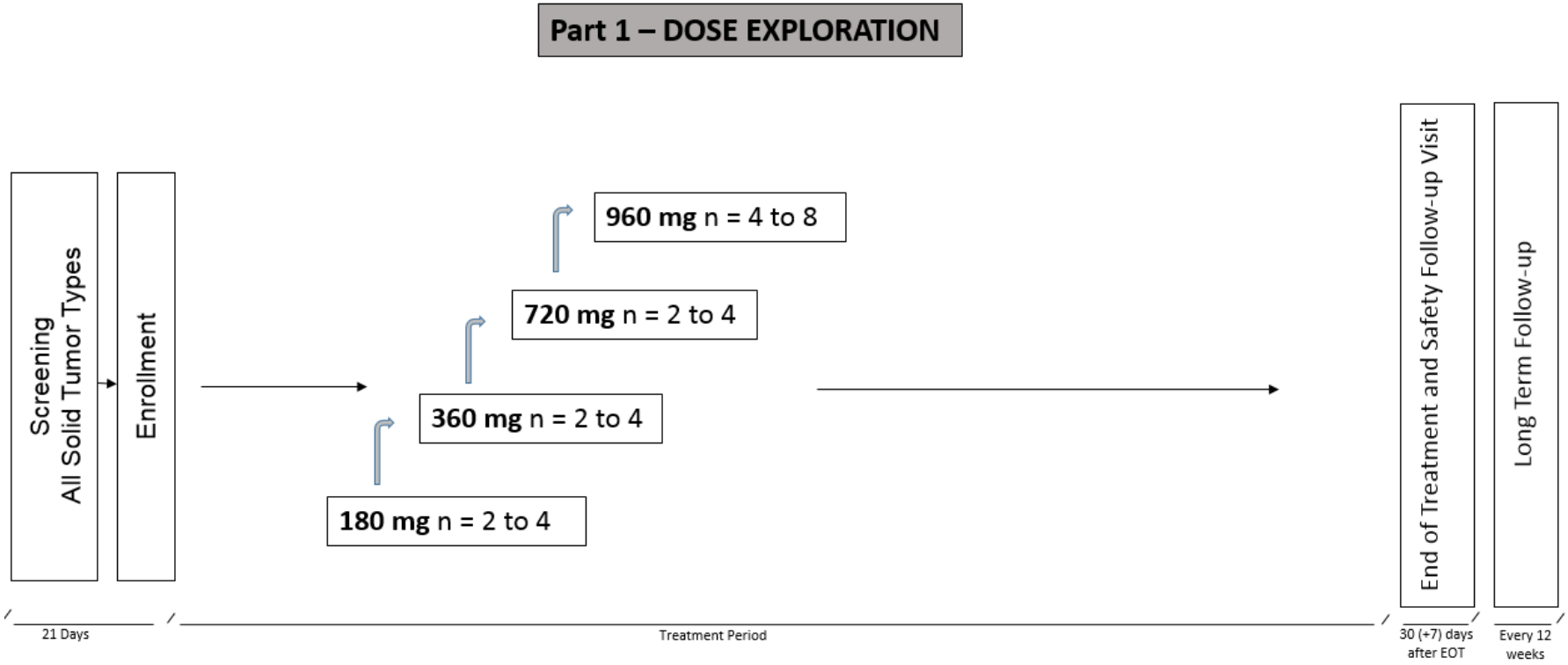
Statistical Considerations: The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or withdraws from the study.

In the dose exploration part, the DLRT will review the safety data after each cohort and make a decision on the next dose level to be explored for the estimate of RP2D/MTD based on a BLRM design.

Descriptive statistics will be provided for selected demographics, safety, PK, efficacy and biomarker data by dose, dose schedule, 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. ORR will be presented with 95% exact CI. Graphical summaries of the data may also be presented.

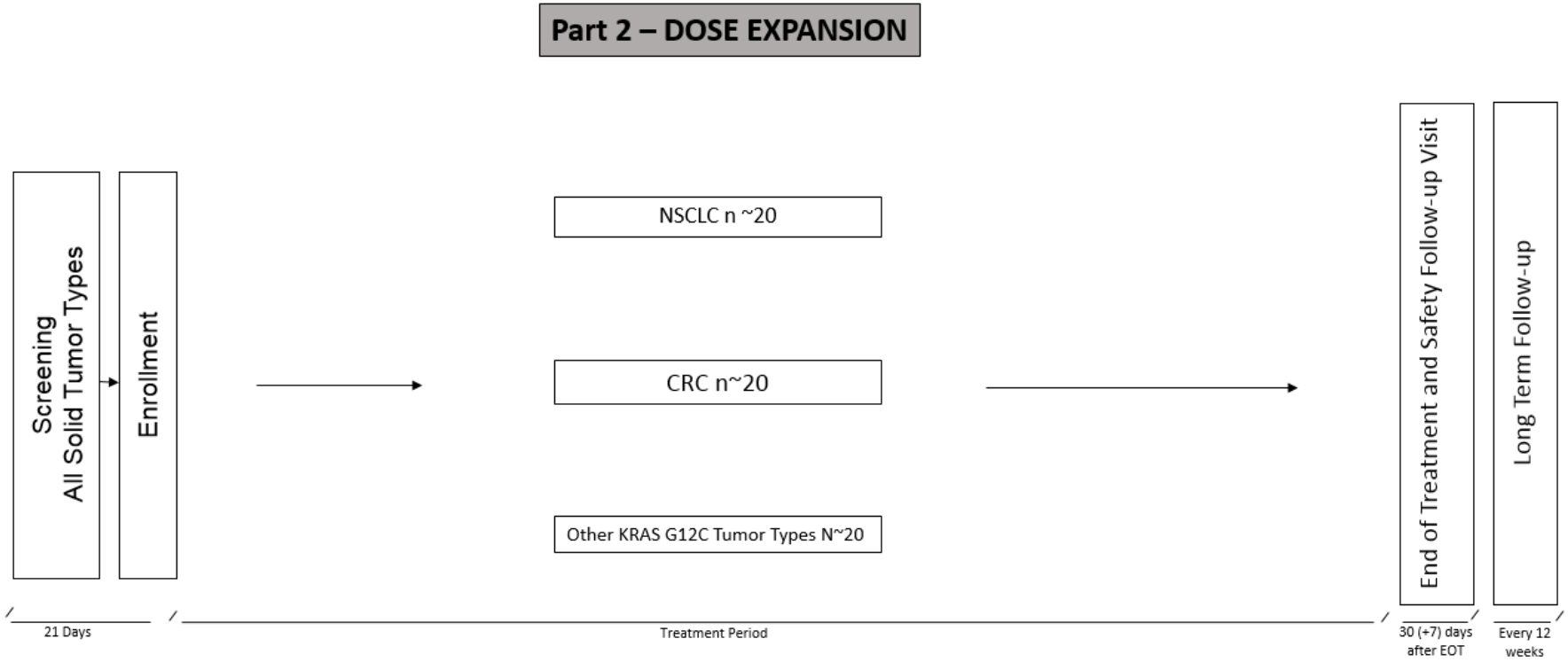
Sponsor: Amgen Inc.

Schema. Study Design and Treatment



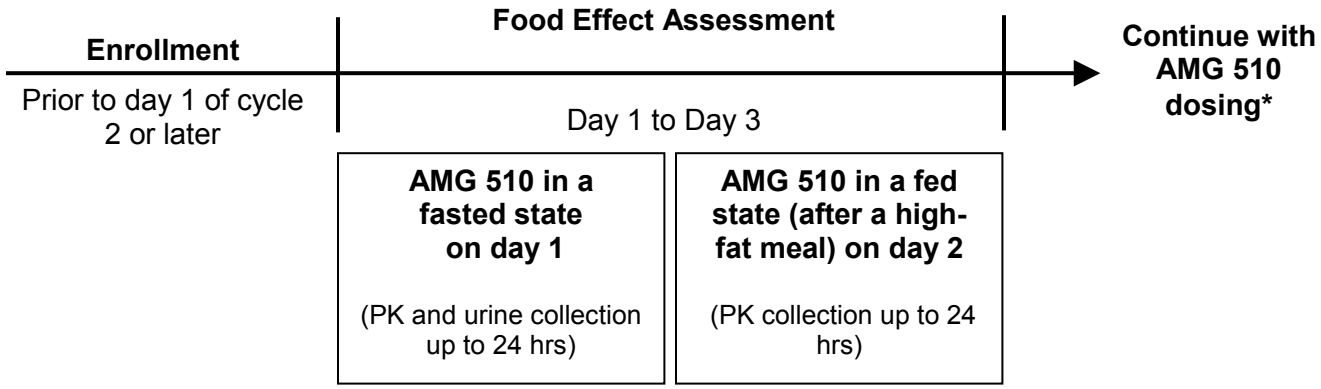
- Repeated **oral** daily dosing with 21 day cycles and no drug holidays
- DLT window of 21 days
- ~4 nominal doses and potential intermediate doses of 270 mg and 540 mg
- Additional subjects may be enrolled in one or more dose levels that have been shown to be safe and tolerable (backfill enrollment)
- Food effect evaluation will be conducted in at least 6 subjects from backfill enrollment in cycle 2 or later
- EOT = End of Treatment

Schema. Study Design and Treatment



- Repeated oral daily dosing with 21 day cycles
- No drug holidays
- EOT = End of Treatment

Schema. Food Effect Assessment



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

Study Glossary

Abbreviation or Term	Definition/Explanation
ANC	absolute neutrophil count
AUC	area under the concentration-time curve from time
ALK	anaplastic lymphoma kinase
BCRP	breast cancer resistance protein
C_{max}	maximum observed concentration
CR	Complete response
CRC	colorectal cancer
CT	Computed tomography
CYP3A	cytochrome P450 3A
DDI	drug-drug interaction
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DILI	drug induced liver injury
DOR	Duration of response
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
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 study
End of Study	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
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 Treatment	defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
Exposure-Response Analysis	mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic [PK] exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic effects, efficacy and safety endpoints
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human

Abbreviation or Term	Definition/Explanation
HNSTD	highest non-severely toxic dose
ICF	informed consent form
ICH	International Conference of Harmonization
IVD	in vitro diagnostic
IR	immediate-release
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
$KRAS^{G12C}$	KRAS protein with a G12C mutation at the protein level
KRAS p.G12C	*KRAS* DNA with a mutation resulting in a G12C mutation at the protein level
MRI	Magnetic resonance imaging
mRNA	messenger ribonucleic acid
NOEL	no observed effect level
NRAS	neuroblastoma RAS viral oncogene homolog
NSCLC	non-small-cell lung carcinoma
ORR	Objective response rate
PD	Progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
P-gp	P-glycoprotein
PCR	polymerase chain reaction
PK	Pharmacokinetic(s)
PO	oral(ly)
PFS	Progression-free survival
PR	Partial respone
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
QD	once daily
QTc	corrected QT (interval)
RAS	rat sarcoma viral oncogene homolog
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 Dose
SD	Stable disease
STD_{10}	severely toxic dose in 10% of animals

Abbreviation or Term	Definition/Explanation
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.
Study Day 1	defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
$t_{1/2,z}$	terminal half-life
T_{max}	time to reach maximum concentration
TGI	tumor growth inhibition
VEGF	vascular endothelial growth factor

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1. OBJECTIVES

1.1 Primary

- Evaluate the safety and tolerability of AMG 510 in adult subjects with *KRAS p.G12C* mutant solid tumors
- Estimate the maximum tolerated dose (MTD) and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) within investigated subject population groups

1.2 Secondary

- Characterize the pharmacokinetics (PK) of AMG 510 following administration as an oral tablet formulation
- To evaluate tumor response assessed by CT or MRI using RECIST 1.1 criteria of AMG 510 as monotherapy in subsets of solid tumors with *KRAS p.G12C* mutation
- To evaluate the effect of food on the oral pharmacokinetics of AMG 510
- To evaluate the relationship between changes in QTc and AMG 510 exposure

1.3 Exploratory

- To explore pharmacokinetic/pharmacodynamic relationships for safety and/or efficacy endpoints
- To characterize AMG 510 excretion in urine
- To identify metabolites of AMG 510 in plasma and urine
- To investigate potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor samples.

2. BACKGROUND AND RATIONALE

2.1 Disease and Background

Worldwide, lung cancer (small cell and non-small cell) and CRC are the first and third most common types of cancer occurring in both men and women (WHO statistics, 2015). It is estimated that in 2018 there will be approximately 234 030 new cases of lung cancer and 140 250 new cases of CRC in the United States alone (American Cancer Society, 2018). The 5-year survival rate for advanced NSCLC cancer is between 1% and 10% depending on the stage. Similarly, the 5-year survival rate for advanced CRC is approximately 11% (American Cancer Society, 2018).

Treatments for both types of advanced cancer typically consist of regimens of cytotoxic chemotherapies, either as a single agent or in combination with other agents. For NSCLC, platinum containing doublets, typically cisplatin/pemetrexed are standard options (NCCN, 2018a). Targeted therapies are also an option where molecular testing has identified mutations in epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), or proto-oncogene tyrosine-protein kinase ROS (*ROS1),* or

expression of programmed death-ligand (PD-L1). In these cases, specific kinase inhibitors or programmed cell death (PD-1) inhibitors can be used.

For unresctable CRC, several cytotoxic agents have demonstrated efficacy, including 5-fluorouracil (5-FU), folinic acid, irinotecan, oxaliplatin and capecitabine (NCCN, 2018b). These drugs are commonly combined in various regimens, and can be further partnered with vascular endothelial growth factor (VEGF) inhibitors or EGFR inhibitors in patients with wild-type *RAS* genes. Other more recent treatment options include the kinase inhibitor regorafenib or a dual agent therapy consisting of trifluridine (a nucleoside metabolic inhibitor) and tipiracil (a thymidine phosphorylase inhibitor).

The *RAS* proto-oncogene has been identified as an oncogenic driver of tumorigenesis in both NSCLC and CRC (Der et al, 1982; Smith et al, 2010; Johnson et al, 2001). The *RAS* family consists of 3 closely related genes that express GTPases responsible for regulating cellular proliferation and survival (Barbacid et al 1987, Simanshu et al, 2017). The RAS proteins, KRAS, Harvey rat sarcoma viral oncogene homolog (HRAS), and neuroblastoma RAS viral oncogene homolog (NRAS) (Harvey, 1964; Chang et al, 1982; Hall et al, 1983; Taparowsky et al, 1983), can be mutationally activated at codons 12, 13, or 61, leading to human cancers. Different tumor types are associated with mutations in certain isoforms of *RAS*, with *KRAS* being the most frequently mutated isoform in most cancers (Prior et al, 2012). Of the *KRAS* mutations, it is estimated that approximately 80% occur at codon 12 (Prior et al, 2012).

The *KRAS p.G12C* mutation is a single guanine to thymine substitution that results in a glycine to cysteine substitution at amino acid position 12. This structural change in the protein results in a defect in the association of GTPase-activating proteins (GAPs), thereby reducing the hydrolysis of GTP by KRAS. The resulting accumulation of active, GTP-bound KRAS leads to enhanced proliferative and survival signaling in tumor cells. The *KRAS p.G12C* mutation has been identified as a putative oncogenic driver in several types of solid tumors including NSCLC (Fernández-Medarde and Santos, 2011) and CRC (Jones et al, 2017). *KRAS p.G12C* mutations have also been identified in other solid tumors such as pancreatic, endometrial, bladder, ovarian, and small cell lung tumors (Zhou et al, 2016; The AACR Project GENIE Consortium, 2017). In both NSCLC and CRC, mutation of *KRAS* is an adverse prognostic factor (Bonanno et al, 2010; Johnson et al, 2013; Jones et al, 2017), and in CRC, the specific *KRAS p.G12C* mutation is associated with poorer prognosis compared to other *KRAS* mutations (Jones et al, 2017). Overall, it is estimated that approximately 13% of lung

adenocarcinoma (including NSCLC), 3% of CRC, and 1% to 2% of numerous other solid tumors (including pancreatic, endometrial, bladder, ovarian, and small cell lung tumors) harbor the *KRAS p.G12C* mutation (Biernacka et al, 2016; Neumann et al, 2009; The AACR Project GENIE Consortium, 2017).

While the role of *KRAS* mutations in human cancers has been known for decades, no anti-cancer therapies specifically targeting *KRAS* mutations have been successfully developed, largely because the protein is intractable for inhibition by small molecules (McCormick, 2016). Therefore, an unmet need currently exists for therapies that can specifically target cancers driven by *KRAS* mutations.

AMG 510 is a small molecule that specifically and irreversibly inhibits the $KRAS^{G12C}$ 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 which covalently modifies the cysteine residue and locks $KRAS^{G12C}$ in an inactive, GDP-bound conformation. This blocks the interaction of KRAS with effectors such as RAF proto oncogene serine/threonine-protein kinase (RAF), thereby preventing downstream signaling, including the phosphorylation ERK (Cully and Downward, 2008; Ostrem et al, 2013; Simanshu et al, 2017). Inactivation of KRAS by RNAi or small-molecule inhibition has previously demonstrated an inhibition of cell growth and induction of apoptosis in tumor cell lines and xenografts harboring *KRAS* mutations (including the *KRAS p.G12C* mutation) (Janes et al, 2018; McDonald et al, 2017; Xie et al, 2017; Ostrem and Shokat, 2016; Patricelli et al, 2016). Studies with AMG 510 have confirmed these in vitro findings and have likewise demonstrated inhibition of growth and regression of cells and tumors harboring *KRAS p.G12C* mutations (Section 5.1). These data suggest that inhibition of *KRAS p.G12C* may have therapeutic benefit for patients with *KRAS p.G12C*-driven cancers. Accordingly, the FIH Study 20170543, will evaluate the safety, tolerability, PK, and efficacy of AMG 510 in subjects with *KRAS p.G12C* mutant advanced NSCLC, CRC, and other solid tumors..

2.1.1 KRAS Pathway and *KRAS p.G12C* Mutation

Mutation of the Kirsten rat sarcoma viral oncogene homolog (*KRAS)* gene *(*Kirsten and Mayer, 1967*)*, a member of the rat sarcoma viral oncogene homolog (RAS) family of proteins, has been identified as an oncogenic driver in numerous types of solid tumors, including lung cancer (Fernández-Medarde and Santos, 2011) and colorectal cancer (CRC) (Jones et al, 2017). Historically, the type of therapy used to treat these solid tumors has depended primarily on the tissue type of the tumor. However, more

recent therapies have been developed that target tumors dependent on specific genetic features of the tumor rather than the tissue type.

While the role of *KRAS* mutations in human cancers has been known for decades (Hobbs et al, 2016), no anticancer therapies targeting *KRAS* mutations have been successfully developed. Thus, an unmet need exists for therapies that can specifically target cancers driven by *KRAS* mutations. AMG 510 is one such small molecule that specifically and irreversibly inhibits the *KRAS p.G12C* mutant which is found in approximately 13% of lung adenocarcinoma (including NSCLC), 3% of CRC, and 1% to 2% of numerous other solid tumors (including pancreatic, endometrial, bladder, ovarian, and small cell lung tumors) harbor the *KRAS p.G12C* mutation (Biernacka et al, 2016; Neumann et al, 2009; The AACR Project GENIE Consortium, 2017). AMG 510 binds to a recently characterized pocket (P2) adjacent to the nucleotide-binding pocket of KRAS and covalently modifies the cysteine residue at position 12. Binding of AMG 510 locks KRAS in the inactive guanosine diphosphate (GDP)-bound conformation and prevents the nucleotide exchange of guanosine triphosphate (GTP) for GDP, thus inhibiting downstream signaling. As inactivation of KRAS has been demonstrated to inhibit cell growth and/or promote apoptosis selectively in tumor cells harboring *KRAS* mutations (Janes et al, 2018; McDonald et al, 2017; Xie et al, 2017; Ostrem and Shokat, 2016; Patricelli et al, 2016), AMG 510 may provide a therapeutic benefit for patients with *KRAS p.G12C*-driven cancers. Accordingly, the first-in-human (FIH) Study 20170543, will evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and efficacy of AMG 510 in subjects with *KRAS p.G12C* mutant advanced solid tumors.

2.2 Amgen Investigational Product Background

AMG 510 is a small molecule that specifically and irreversibly inhibits the $KRAS^{G12C}$ 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 which covalently modifies the cysteine residue and locks $KRAS^{G12C}$ in the inactive GDP-bound conformation. This blocks the interaction of KRAS with effectors like RAF, thus preventing downstream signaling, including the phosphorylation of ERK (Ostrem et al, 2013; Simanshu et al, 2017). Inactivation of KRAS through a small molecule inhibitor has previously demonstrated an inhibition of cell growth and induction of apoptosis in tumor cell lines and xenografts with the *KRAS p.G12C* mutation (Ostrem and Shokat 2016; Patricelli, Janes et al. 2016; Janes, Zhang et al. 2018). Likewise, studies of AMG 510 have demonstrated inhibition of growth and regression of

cells and tumors harboring *KRAS p.G12C* (Section 2.2.1). 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 Study 20170543, will evaluate the safety and efficacy of AMG 510 in subjects with *KRAS p.G12C* mutant advanced NSCLC, CRC, and other solid tumors

2.2.1 AMG 510 Pre-clinical

In vitro AMG 510 inhibited nucleotide exchange of recombinant mutant $KRAS^{G12C/C118A}$ (half maximal inhibitory concentration, IC_{50} = 0.09 μM), but had minimal effect on $KRAS^{C118A}$, which is wildtype at G12. In cells, AMG 510 covalently modified $KRAS^{G12C}$ and inhibited KRAS signaling as measured by phosphorylation of ERK1/2 in all *KRAS p.G12C*-mutant cell lines tested (IC_{50} values from 0.01 to 0.12 μM), but did not inhibit phospho-ERK1/2 in cell lines with various other *KRAS* mutations. AMG 510 also impaired viability in all but one *p.G12C*-mutant cell lines (IC_{50} values from 0.004 to 0.032 μM), but did not affect the viability of cell lines that did not harbor the *KRAS p.G12C* mutation. The cellular k_{inact} and K_i values for AMG 510 were also experimentally determined in MIA PaCa-2 cells to be 0.00133 sec^{-1} and 6.97×10^{-7} M, respectively, with k_{inact}/K_i ratio of 1.9×10^{3} M^{-1} sec^{-1}.

In vivo AMG 510 covalently modified $KRAS^{G12C}$ and significantly inhibited phospho-ERK1/2 in human *KRAS p.G12C* MIA PaCa-2 T2 pancreatic and *KRAS p.G12C* NCI-H358 NSCLC tumor xenografts in mice in a dose-dependent manner at doses as low as 1 mg/kg in the MIA PaCa-2 T2 model. After a single, 10 mg/kg dose in mice bearing MIA PaCa-2 T2 tumors, exposure of AMG 510 peaked at 0.5 hours, followed closely by maximal inhibition of phospho-ERK1/2 by 1 hour to 2 hours. Covalent modification of $KRAS^{G12C}$ by AMG 510 tracked with inhibition and maximal modification occurred after 2 hours. Significant inhibition and modification of $KRAS^{G12C}$ persisted for 48 hours after a single, 10 mg/kg dose. In tumor xenograft studies AMG 510 significantly inhibited the growth of MIA PaCa-2 T2 and NCI-H358 tumors at doses as low as 3 mg/kg and achieved 62% and 49% regression, respectively, at 100 mg/kg. Notably AMG 510 had no effect on SW480-1AC (*KRAS p.G12V*) tumor xenografts at 100 mg/kg and did not impact body weight in any study.

2.2.2 Pharmacokinetics

AMG 510 was characterized in vitro and in vivo preclinical studies. AMG 510 exhibited moderate to high clearance (CL), moderate volume of distribution (V_{ss}), and terminal elimination half-life ($t_{1/2,z}$) of 0.34 to 0.71 hours in animal species. The oral bioavailability

of the suspension formulation was variable, ranging from 3.3 to 47% across the species tested. AMG 510 has moderate binding to plasma proteins in all species including humans. AMG 510 did not preferentially distribute into red blood cells in mouse, rat, dog, and human whereas it was preferentiallydistributed into red blood cells in monkey. These data were used to predict the human AMG 510 PK parameters

AMG 510 was predominantly eliminated in preclinical species in vivo through CYP3A-catalyzed formation of the metabolite, M24. M24 has >1000-fold less pharmacological activity than its parent, AMG 510. AMG 510 was also a substrate of P-glycoprotein in vitro.

AMG 510 has a potential to cause CYP3A-mediated drug-drug interaction (DDI) due to reversible and irreversible time-dependent inhibition of CYP3A and induction of CYP3A4 in vitro. M24 also has a potential to cause CYP3A-mediated drug-drug interactions due to reversible and irreversible time-dependent inhibition of CYP3A and induction of CYP3A4 in vitro. In vitro, AMG 510 was also shown to be an inhibitor of CYP2C8 and CYP2D6, but not an inhibitor of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP2E1. M24 was an inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. In vitro, AMG 510 was shown to be an inducer of CYP2B6, CYP2C8, CYP2C9, and CYP2C19, while M24 was an inducer of CYP2B6, CYP2C8, CYP2C9 and CYP2C19.

In vitro, AMG 510 is a P-gp substrate, thus active transport by P-gp may affect AMG 510 absorption and elimination. AMG 510 is not a BCRP substrate. Additionally, AMG 510 and its metabolite M24 was identified as an inhibitor of human MATE1. AMG 510 was also an inhibitor of human OAT3, OATP1B1, MATE2-K and P-gp. Incomplete inhibition was observed up to the highest test concentration for human OAT1, OCT1, OATP1B3 and BCRP, suggesting weak inhibition. M24 was an inhibitor of human OAT1, OAT3, OATP1B1, OATP1B3, and P-gp. Incomplete inhibition was observed up to the highest test concentration for human MATE2-K and BCRP, suggesting weak inhibition.

Based on current in vitro data, AMG 510 has a potential to interact with CYP3A4 and MATE1. The DDI potential for other enzymes and transporters is expected to be low.

2.2.3 Toxicology

Animal toxicology studies have been completed in both the rat and dog and support development of AMG 510 for treatment of *KRAS p.G12C*mutated tumors. AMG 510 was well tolerated in the GLP 28-day rat toxicology study at 0, 10, 30, and 200 mg/kg and in the GLP 28 day dog toxicology study at 0, 10, 30, and 300 mg/kg. Key AMG 510-related

changes in the rat were minimal to mild and included kidney tubular epithelial degeneration/necrosis; increased spleen weight, increased leukocytes; and a decrease in red blood cell (RBC) mass (hemoglobin, RBC count, and hematocrit) that was associated with changes in reticulocytes and RBC indices. In the rat, AMG 510-related degeneration/necrosis of renal tubule epithelium primarily affected tubules within the outer segment of the outer medulla and was characterized by sloughing of degenerative/necrotic epithelial cells, tubular dilatation, and/or accumulation of eosinophilic material within the tubule. Reversibility data is pending in the rat. The degeneration/necrosis observed in the kidney is expected to be fully reversible based on the minimal to mild severity, the absence of tubular basement membrane damage, and the normal regenerative capacity of the renal tubular epithelium. Key AMG 510-related changes in the dog consisted of a minimal to mild decrease in RBC mass associated with decreased reticulocytes. Taken together, the AMG 510-related decrease in RBC mass and reticulocytes in the rat and dog are most likely due to red blood cell/reticulocyte destruction and not decreased hematopoietic production, given the absence of light microscopic changes in the bone marrow in dog and the increased bone marrow erythroid cellularity in a few rats. The decreases in RBC mass and reticulocytes are expected to be reversible based on the normal regenerative capacity of the hematopoietic system, and the absence of overt bone marrow toxicity (eg, hypocellularity).

AMG 510 nonclinical safety studies have not identified cardiovascular concerns. Clinically significant interaction with the hERG channel are not expected over the proposed clinical dose range (hERG IC50 54.8 μM). AMG 510 at doses up to 300 mg/kg did not result in changes to ECG or hemodynamic parameters in a cardiovascular safety pharmacology study in telemetered dogs or in a 28-day toxicology study. In exploratory genetic toxicology studies, AMG 510 was not mutagenic in the Ames bacterial mutagenicity assay but was positive for clastogenicity in vitro. AMG 510 was not phototoxic in vitro.

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% of animals (STD10) in rats was > 200 mg/kg and the highest non-severely toxic dose (HNSTD) in dogs was ≥ 300 mg/kg. There was minimal toxicity at exposures up to 9-fold above those expected in humans at the highest therapeutic dose. Overall, the results of

the nonclinical safety studies support the initiation of AMG 510 clinical trials and the initial clinical plan.

2.3 Risk Assessment

There are no identified risks associated with the administration of AMG 510. Based on nonclinical toxicity studies of AMG 510, the potential risks of AMG 510 include renal toxicity, anemia, leukocytosis, and splenomegaly. Clinical signs and symptoms of these potential risks, along with safety laboratories, will be monitored during the study to ensure subjects' safety.

Please refer to the Investigator's Brochure, section 7 for a description of important potential risks.

2.4 Dose Selection Rationale

The proposed AMG 510 doses are 180, 360, 720, and 960 mg administered once daily (QD) orally (PO). During dose escalation (Part 1) and dose expansion (Part 2), AMG 510 will be given QD PO for a treatment cycle of 21 days in length that include 21 administrations of AMG 510. The planned dose level(s) for dose expansion (MTD/RP2D) will be determined based on data collected during dose escalation.

The proposed clinical starting dose of 180 mg administered QD PO is based on the current guidance for starting dose of anti-cancer small molecule drugs (ICH S9) using the methodology described by the Food and Drug Administration for calculating the human equivalent dose (HED) on a body surface area basis (FDA, 2005). The rat severely toxic dose in 10% of animals (STD_{10}) and the dog highest non-severely toxic dose (HNSTD) were 200 mg/kg/day PO and 300 mg/kg/day PO, respectively, as noted in the 28-day repeat-dose GLP toxicology studies. The proposed starting dose was roughly the maximum recommended starting dose of 195 mg/day PO, which is based on the lower value of $1/10^{th}$ the HED for the rat STD_{10} (195 mg/day PO) and $1/6^{th}$ the HED for the dog HNSTD (1622 mg/day PO). To estimate AMG 510 exposures in humans, AMG 510 human pharmacokinetics (PK) parameters were predicted using allometric scaling of PK parameters for clearance and volume obtained from nonclinical studies in mice, rats, monkeys, and dogs and absorption constant and oral bioavailability following oral tablet administration of AMG 510, the same tablet formulation to be used in this clinical study. At the starting dose of 180 mg administered QD PO, the predicted exposure margins of steady-state maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) exposures relative to the rat STD_{10} are 62-fold and 20-fold, respectively. The predicted exposure margins of steady-state C_{max} and AUC

exposures relative to the dog highest severely toxic dose (HNSTD) are estimated at 50-fold and 12-fold, respectively, at the starting dose administered orally once daily.

The highest planned dose is 960 mg QD PO. The exposure margins for the predicted human steady state AUC and C_{max} exposures of this dose are 12-fold and 4-fold, respectively relative to rat STD_{10} and 9-fold and 2-fold, respectively relative to dog HNSTD. Safety and tolerability data from prior dose levels will guide the dose escalations and the planned top dose for AMG 510 in the dose escalation phase. The maximum tolerated dose (MTD) identified from the dose escalation phase will inform the dose expansion phase.

Efficacious doses were predicted with 2 PK/tumor growth inhibition (TGI) models that describe the anti-tumor activity of AMG 510: (1) a tumor stasis model that estimates human exposures to cause tumor stasis (i.e. no net tumor growth) based on PK and TGI of MIA-PaCa-2 T2 tumor xenograft mice treated with AMG 510 and (2) a tumor regression model that utilizes clinical pancreatic cancer data and PK and TGI in AMG 510-treated MIA-PaCa-2 T2 xenograft mice to predict the treatment effects of AMG 510 on tumor growth dynamics in humans. Consolidating the results from both models, the minimal efficacious dose for AMG 510 in humans was predicted to be between 30 and 240 mg QD PO.

Integrating the toxicology, pharmacology, human PK and efficacious dose predictions, the starting dose of 180 mg QD is expected to be safe as well as potentially efficacious.

2.5 Clinical Hypotheses

The following hypotheses will be tested with this clinical protocol.

- At least one dose level of AMG 510 administered orally is expected to achieve acceptable safety and tolerability in subjects with advanced *KRAS p.G12C*solid tumors
- A favorable PK profile will be achieved with AMG 510 administered orally.
- Objective responses will be observed at a dose level that achieves acceptable safety and tolerability.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study to evaluate safety and tolerability of AMG 510 in subjects with advanced *KRAS p.G12C*mutant solid tumors. The study will be conducted at approximately 25 sites in Australia, United States (US), Canada, Brazil, France, Germany, China, Japan, and

South Korea. Other countries or regions may participate. AMG 510 will be evaluated as an oral therapeutic. The study will be conducted in 2 parts: Part 1 – Dose Exploration and Part 2 – Dose Expansion. Part 1 is aimed at evaluating the safety, tolerability, PK and pharmarcodynamics of AMG 510 and determining the MTD of repeat daily (QD) dosing schedule in subjects with advanced *KRAS p.G12C*mutant solid tumors using a Bayesian logistics regression model (BLRM) design (Neuenschwander, Branson, & Gsponer, 2008). The dose expansion part of the study (Part 2) can open once the MTD and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) has been determined in Part 1. The dose exploration part of the study will consist of approximately 50 subjects and the dose expansion part will consist of approximately 60 additional subjects, including at least 3 groups with specific tumors harboring *KRAS p.G12C*mutations (non-small cell lung cancer [NSCLC], colorectal cancer [CRC], and all other solid tumors). Different schedules can be used in the dose expansion part based on clinical and PK data from all parts of the dose exploration. The DLT evaluation period will be at least 21 days. Based on emerging clinical efficacy data, the groups explored in the expansion part can be modified. Administration of AMG 510 (in part 1 and part 2) may continue until evidence of disease progression, intolerance to study medication, or withdrawal of consent.

Dose Exploration – Part 1

Dose exploration cohorts will estimate the MTDs, safety, tolerability, PK, and pharmacodynamics of different doses of AMG 510 in subjects with advanced *KRAS p.G12C* mutant solid tumors. Subjects will receive AMG 510 daily administered orally. Enrollment into the dose exploration cohorts may be from any eligible *KRAS p.G12C*mutant soild tumor type. Dose escalation will begin with 2-4 subjects treated at the lowest planned dose level of 180 mg. Dose escalation will follow the planned Study Schema schedule with 2-4 subjects treated in each cohort. If no DLT is observed, dose escalation will continue to the next planned dose cohort as per Table 1. Once a subject experiences a DLT, dosing for subsequent cohorts will be recommended using the dose level recommendation from the Bayesian Logistic Regression Model (BLRM). After each cohort, the model's recommended MTD dose level for evaluation is the dose level with the highest probability of the target toxicity probability interval (TPI), but with a less than 0.25 probability of an excessive TPI. The target TPI is (0.20, 0.33], and a TPI of (0.33, 1.00] is defined as excessive. The decision to advance to the next dose level will be recommended by the Dose Level Review Team (DLRT) using the dose level

recommendation from BLRM, as appropriate, and by evaluating available safety data, laboratory, and PK information.

Intra-subject dose escalations are allowed in this study. Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle once the next dose cohort has been deemed safe by the DLRT and after consultation with the sponsor if:

- no DLT has been reported for this subject during or after completion of the DLT period
- the subject has not experienced any ≥ grade 2 adverse events (deemed treatment related by the investigator) during treatment

Subjects who do not proceed to a higher dose may receive extra cycles at the original dose.

Dose exploration will continue until any of the following events.

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 DLT-evaluable subjects)
- The MTD is identified, BLRM recommends a dose level which already has 6 DLT-evaluable subjects

No more than 50 subjects will be enrolled to the dose escalation cohorts. Approximately 30 subjects will be needed to estimate the MTD. In order to better estimate the RP2D and to better characterize the safety, efficacy and pharmacodynamics for AMG 510, an additional 20 subjects may be enrolled in one of more dose levels that have been deemed to be safe and tolerable, defined as backfill enrollment. Subjects in backfill enrollment will be allowed to proceed to higher dose levels when the higher dose levels have been deemed safe and tolerable. This backfill enrollment may be concurrent with dose escalation to identify the MTD.

Table 1. Planned Escalation Dose *Levels

Cohort	Dose (mg)
1	180
2	360
3	720
4	960

*Potential intermediate doses of 270 mg and 540 mg

Food effect will be evaluated in cycle 2 or later in at least 6 subjects from backfill enrollment. On day 1 of the cycle in which the assessment will be conducted, subjects

will receive their dose of AMG 510 with approximately 240 mL (8 ounces) of water under fasted conditions (no food or liquids, except water) for ≥10 hours prior to ingesting their dose of AMG 510 at the clinic. The subjects will fast overnight again (no food or liquids, except water for ≥10 hours) before returning to the clinic on day 2 to ingest their dose of AMG 510 after eating a standardized high-fat, high calorie meal. Subjects should eat the meal in 25 minutes or less; AMG 510 should be administered 30 minutes after the start of the meal and after at least 5 minutes of rest. Carryover of AMG 510 exposure from a prior dose is expected to be minimal based on the predicted half-life of AMG 510. For both days, no food is allowed for at least 3 hours following AMG 510 dosing. Additional water can be consumed as desired, except for 1 hour prior to and 1 hour after AMG 510 dosing. PK will be collected prior to dosing and at various time points over a 24-hour period after dosing on both days. Urine will be collected for the 24-hour period following day 1 dosing.

Dose Expansion – Part 2

Upon completing the dose exploration part of the study and depending on data obtained, dose expansion may proceed with three groups consisting of subjects with *KRAS p.G12C*mutant solid tumors:

1. Group 1 (NSCLC) - subjects with advanced *KRAS p.G12C*mutant NSCLC
2. Group 2 (CRC) - subjects with advanced *KRAS p.G12C*mutant CRC
3. Group 3 (Other) - subjects with advanced *KRAS p.G12C*mutant solid tumor types other than the tumor types specified in Groups 1 and 2

Dose expansion in all three groups may be done concurrently.

A final estimate of the MTD and RP2D using BLRM will be evaluated and confirmed utilizing all DLT-evaluable subjects from the dose escalation and the dose expansion cohorts. For definition of DLT-evaluable, see Section 3.3.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1

3.2 Number of Sites

This study will be conducted at approximately 25 sites in Australia, United States, Canada, Brazil, France, Germany, China, Japan, and South Korea. Additional countries or sites may be added if deemed necessary.

Sites that do not enroll subjects into an open cohort within 6 months of site initiation may be closed or replaced.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

It is anticipated that up to 110 subjects will be enrolled in the study. Up to 50 subjects will be enrolled in dose escalation cohorts and up to 60 subjects will be enrolled in the dose expansion cohorts. The rationale for the number of subjects is provided in Section 10.2.

During dose escalation, a subject that is not DLT-evaluable will be replaced with another subject to the same dose level. A subject is DLT-evaluable if either of the following occurs:

- Subject experienced a DLT or
- Subject does not experience a DLT and subject received at least 80% of the planned doses of investigational product within the first treatment cycle (ie, 21 days)

Subjects will not be replaced after end of the DLT period.

3.4 Estimated Study Duration

3.4.1 Study Duration for Subjects

The duration of this study will be approximately 2.5 years, with about 24 months for enrollment (a maximum of 12 months for the dose escalation cohorts, and 12 months for the dose expansion cohort) and 6 months protocol treatment period.

3.4.2 End of Study

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis; the primary analysis will occur when target enrollment in dose escalation and dose expansion is complete and each subject either completes 6 months on study or withdraws from the study.

End of Study: the time when the last subject is assessed or receives an intervention for evaluation in the study. The final analysis will occur at this time.

4. SUBJECT ELIGIBILITY

4.1 Inclusion Criteria

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

102. Men or women ≥ 18 years old

103. Pathologically documented, locally-advanced or metastatic malignancy with, *KRAS p.G12C*mutation identified through DNA sequencing. Subjects must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.

104. Part 1 (Dose Exploration) – Subjects willing to provide archived tumor samples (fresh frozen sample or formalin fixed, paraffin embedded [FFPE] sample collected within 5 years) or willing to undergo pre-treatment tumor biopsy.

105. Part 2 (Dose Expansion) – Willing to undergo pre-treatment tumor biopsy. Subjects can be allowed to enroll without undergoing tumor biopsy upon agreement with Investigator and the Medical Monitor if tumor biopsy is not feasible.

106. Measurable or evaluable disease per RECIST 1.1 criteria (Appendix D).

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

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

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

110. QTc ≤ 470 msec (based on average of screening triplicates)

111. 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 ≥ 9 g/dL

112. Adequate renal laboratory assessments, as follows:

- Estimated glomerular filtration rate based on MDRD (Modification of Diet in Renal Disease) calculation ≥ 60 ml/min/1.73 m^2

113. Adequate hepatic laboratory assessments, as follows:

- AST < 2.5 x ULN (if liver metastases are present, ≤ 5 x ULN)
- ALT < 2.5 x ULN (if liver metastases are present, ≤ 5 x ULN)
- Alkaline phosphatase < 2.0 x ULN (if liver or bone metastases are present, < 3.0 x ULN)
- Total bilirubin < 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)

114. Adequate coagulation laboratory assessments, as follows:

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

Food Effect Assessment – Specific Inclusion Criteria

115. Subject able to eat a standardized high-fat, high-caloric meal within 25 minutes

116. Subject able to fast for ≥10 hours

117. Subject able to handle collection of his/her urine over a 24 hour period.

Part 2 – Dose Expansion (Criteria 101 to 114, except criterion 104)

Non-small Cell Lung Cancer – Specific Inclusion Criteria

118. Pathologically documented, definitively diagnosed *KRAS p.G12C*mutant NSCLC

Colorectal Cancer – Specific Inclusion Criteria

119. Pathologically documented, and definitively diagnosed *KRAS p.G12C* mutant CRC

Other Solid Tumor Types – Specific Inclusion Criteria

Pathologically documented, definitively diagnosed, *KRAS p.G12C*mutant advanced solid tumor

4.2 Exclusion Criteria

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 ≤ 2; b) on stable doses of dexamethasone, if applicable; and c) follow-up MRI shows no new lesions appearing

202. History or presence of hematological malignancies unless curatively treated with no evidence of disease ≥ 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 alimentation, uncontrolled inflammatory GI disease (eg, Crohn's disease, ulcerative colitis)

205. Active infection requiring intravenous (IV) antibiotics within 1 weeks of study enrollment (day 1)

206. Positive Hepatitis B Surface Antigen (HepBsAg) (indicative of chronic Hepatitis B), positive Hepatitis total core antibody with negative HepBsAg (suggestive of occult hepatitis B) or detectable Hepatitis C virus Ribonucleic acid (RNA) by PCR (indicative of active Hepatitis C - screening is generally done by Hepatitis C Antibody (HepCAb), followed by Hepatitis C virus RNA by PCR if HepCAb is positive)

207. Known positive test for HIV

208. Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 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

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. All herbal medicines (eg, St. John's wort), vitamins, and supplements consumed by the subject within the 30 days prior to receiving the first dose of AMG 510, and continuing use if applicable, will be reviewed by the Principal Investigator and the Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgment is required for subject participation

214. Major surgery within 28 days of study day 1

215. Men and women of reproductive potential who are unwilling to practice acceptable methods of effective birth control while on study through 1 week (women) or 90 days (men) after receiving the last dose of study drug. Acceptable methods of effective birth control include sexual abstinence (refraining from heterosexual intercourse; men, women); vasectomy; tubal ligation; or a condom with spermicide (men) in combination with barrier methods, hormonal birth control or IUD (women)

216. Women who are lactating/breast feeding or who plan to breastfeed while on study through 1 week after receiving the last dose of study drug.

217. Women with a positive pregnancy test.

218. Women planning to become pregnant while on study through 1 week after receiving the last dose of study drug

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

220. Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge

221. 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

222. 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

223. Use of known cytochrome P450 (CYP) 3A4 sensitive substrates (with a narrow therapeutic window), within 14 days or 5 half-lives (whichever is longer) 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

224. Use of strong inhibitors of CYP3A4 or P-gp within 14 days or 5 half-lives (whichever is longer) or grapefruit juice or grapefruit containing products within 7 days prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor.

225. Use of strong inducers of CYP3A4 within 14 days or 5 half-lives (whichever is longer) within 7 days prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor.

5. 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 (see Section 11.2). All subjects or legally acceptable representatives must personally sign and date the informed consent form before commencement of study-specific activities/procedures. Adverse Events are to be collected for a subject once they are enrolled in the study. Subject is considered enrolled when all eligibility criteria are met and subject is administered the first dose of AMG 510.

The Investigator is to document the enrollment decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (at least 21 days prior to first dose of AMG 510) receives a unique subject identification number before any study 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.

5.1 Treatment Assignment

An Amgen representative will notify the site in writing when a cohort is open to screen new subjects.

All screening tests and procedures must be performed within 21 days of study day 1, unless specified otherwise in the study procedures listed in Section 7. Once the site has established subject eligibility, a site representative will submit (via email) a completed subject Eligibility Worksheet to an Amgen representative. The Amgen representative will acknowledge receipt of the paperwork and assign the AMG 510 dose level to confirm enrollment for that individual subject. The investigator or designee is responsible for ensuring that confirmation of enrollment from Amgen (including subject number, dose assignment and enrollment date) has been received prior to administration of study medication on day 1. A subject is considered enrolled on study day 1 when the investigational product, AMG 510, is first administered.

The treatment assignment date is to be documented in the subject's medical record and on the enrollment case report form (CRF).

To acquire additional safety, efficacy, and pharmacodynamic data to better fully inform the RP2D, an additional 20 subjects may be enrolled in one or more dose levels that have been shown to be safe and tolerable. For the purposes of dose-escalation decisions, these subjects will not be included as part of the DLT-evaluable population. Intra-subject dose escalations is allowed for these additional subjects. When the subject completes the DLT period the subject may proceed to a higher dose level for the following treatment cycle once the next dose cohort has been deemed safe by the DLRT and after consultation with the sponsor as described in Section 3.1. For subjects participating in food effect evaluation, intra-subject dose escalation should not occur for at least 5 days before or during the food effect evaluation.

6. TREATMENT PROCEDURES

AMG 510 is the only investigational product administered orally in this study. A separate manual containing detailed information regarding the storage and administration of AMG 510 will be provided. Refer to the Investigational Product Instruction Manual (IPIM).

6.1 Investigational Product

6.1.1 Amgen Investigational Product AMG 510

AMG 510 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. AMG 510 will be provided as 30 mg and 120 mg tablets and will be packaged in bottles of 30 tablets. A diary will be provided for subjects to record their adherence to the oral medication.

6.1.1.1 Dosage, Administration, and Schedule

AMG 510 will be administered orally daily and repeatedly without any drug holidays. The effects of overdose of AMG 510 are not known. 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 2. Subjects will take AMG 510 at home on non-clinic visit days. AMG 510 must be administered in the fasted state (no food or liquids, except water, 2 hours before to 1 hour after dosing). On cycle 1 day 1, cycle 1 day 8, and cycle 2 day 1, subjects should eat a standard meal at least 2 hours before dosing. Subjects may eat the standard meal at home before clinic visit or in clinic.

Subjects participating in the food effect assessment will receive AMG 510 in the fasted state on day 1 and fed state on day 2. Subjects in the fasted state will receive AMG 510 on an empty stomach (no food or liquids, except water) following an overnight fast of ≥ 10 hours at home prior to clinic visit for dosing. Subjects will receive AMG 510 with approximately 240 mL (8 ounces) of water. Water can be allowed as desired except for 1 hour before and 1 hour after AMG 510 administration. No food or liquid (except water) will be allowed for at least 3 hours post-dose.Subjects in fed state will be fasted overnight for at least 10 hours prior to consuming a high fat meal preferably in the clinic. Subjects should start the recommended meal approximately 0.5 hours prior to dose administration. Subjects should consume the entire meal in 25 minutes or less. AMG 510 should be administered approximately 30 minutes after the start of the meal with approximately 240 mL (8 ounces) of water. Water can be allowed as desired except for 1 hour before and 1 hour after AMG 510 administration. No food or liquid (except water) will be allowed for at least 3 hours post dose. See specific assessments for feed effect evaluation in Table 2..

6.1.1.2 Dose-cohort Escalation and Stopping Rules

After all DLT-evaluable subjects within a cohort have completed the DLT window, a DLRM will be held to review data, monitor safety, and recommend dose change

decisions. The review team will be composed of the investigators, Amgen Medical Monitor, Amgen Global Safety Officer or designated safety scientist, Amgen Early Clinical Development Manager, and Biostatistics representative. Additional members may be added as needed (e.g. 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 decision 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 global safety officer or designated safety scientist, and all actively screening and enrolling investigators or their qualified sub-investigator designee. The team may recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), continuation or delay in dosing, repetition or expansion of a cohort, de-escalation to a lower dose, or termination of the study. The Amgen medical monitor and Global Safety Officer or designee 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. All available study data including demographics, medical history, concomitant medications, AEs, electrocardiograms (ECGs), vital signs, laboratory results, and emerging PK or pharmacodynamics data will be reviewed. Data to be reviewed may be unqueried.

The dosing schedule is described by a schema in the protocol synopsis.

6.1.1.2.1 DLT Definition

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

The grading of AEs will be based on the guidelines provided in the CTCAE version 4.0. 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 nausea for 3 days or more despite optimal medical support
- Any other grade ≥ 3 AE

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

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

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 with a favorable response to treatment, an option to continue at the same dose level or 1 dose level below that which the toxicity occurred can be considered. If deemed appropriate by the investigator in conjunction with the sponsor, AMG 510 treatment can resume once any non-hematological toxicity returns to the subject's baseline value or grade ≤ 1 and subject meets the following hematological requirements: ANC ≥ 1.0 x 10^9/L, platelet count ≥ 75 x 10^9/L and hemoglobin ≥ 9 g/dL. Subjects must not have received a platelet transfusion for at least 7 days prior to assessing if re-exposure to AMG 510 can occur.

If a subject is noted to have ≥ grade 3 thrombocytopenia, grade 4 neutropenia, grade 4 anemia, grade 4 leukocytosis, or ≥ grade 3 non-hematological toxicity attributable to AMG 510 at any point during study treatment, AMG 510 administration will be stopped immediately. A repeat blood collection for hematology is to be performed within 3 days. AMG 510 treatment can resume once subjects meet the following hematological requirements: ANC ≥ 1.0x 10^9/L, platelet count ≥ 75 x 10^9/L and hemoglobin ≥ 9 g/dL, leukocytosis < grade 3 and the non-hematological toxicity returns to the subject's baseline value or grade ≤ 1.

Subjects requiring more than 2 weeks to recover from grade ≥ 3 toxicities will be withdrawn from the study.

6.2 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], AST,ALT, TBIL) or INR or signs/symptoms of hepatitis may meet the criteria for withholding of investigational product. Withholding is either permanent or conditional depending upon the clinical circumstances discussed below as specified in the (FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

6.3 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.5.

Concomitant use of MATE1 substrates with AMG 510 may result in increase in systemic concentrations of a MATE1 substrate as AMG 510 has a potential to inhibit MATE1. Gastric acid controllers may reduce the exposure to AMG 510. Consider the risks and benefits of concomitant use. Monitor subjects receiving a MATE1 substrate or gastric acid controller with AMG 510.

6.4 Product Complaints

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

This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

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

6.5 Excluded Treatments, Medical Device Use, and/or Procedures During Study Period

Any known strong inhibitors of cytochrome P450 (CYP) 3A4, P-gp, grapefruit juice or grapefruit containing products that were not reviewed and approved by the principal investigator and the Amgen medical monitor

Any known strong inducers of cytochrome P450 (CYP) 3A4, P-gp, grapefruit juice or grapefruit containing products that were not reviewed and approved by the principal investigator and the Amgen medical monitorHerbal medicines (eg, St. John's wort), vitamins, and supplements that were not reviewed and approved by the principal investigator and the Amgen medical monitor

Any known cytochrome P450 (CYP) 3A4 sensitive substrates (with a narrow therapeutic window), that were not reviewed and approved by the principal investigator and the Amgen medical monitor

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 2. Schedule of Assessment: Part 1 Dose Exploration and Part 2 Dose Expansion

	Screening	Treatment																															EOT	SFU	LTFU
Cycle		1																					2						3,5 (g)	4,6 (g)	QC (g)	Q2C			
Day	-21 to 1	1								2		8							9		15		1					8	1	1	1	1			
Hours (relative to dosing)		pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	pre	0	0.25	0.5	1							
GENERAL & SAFETY																																			
Informed consent	X																																		
Medical history & height	X																																		
Physical exam & weight	X	X								X		X									X		X					X	X	X	X			X	
ECOG	X	X								X		X									X		X					X	X	X	X			X	
Vital signs	X	X								X		X									X		X					X	X	X	X			X	
ECG (a)	X(a)	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	
Con medications	X	X	←==========																																	
Adverse events	X	X	←==========																																	
LABORATORY																																			
Chemistry	X	X										X									X		X					X	X	X	X	X			
HbA1c	X																												X(h)				X(h)		
Hematology	X	X										X									X		X					X	X	X	X				
Coagulation	X	X										X									X		X					X	X	X	X				
Urinalysis	X	X																					X						X			X	X		
Serum pregnancy test	X																												X			X	X		
HBV surface antigen & HCV Ab	X																																		

Footnotes defined on last page of the table

Table 2. Schedule of Assessment: Part 1 Dose Exploration and Part 2 Dose Expansion

	Screening	Treatment																																EOT	SFU	LTFU
Cycle		1																						2						3,5 (g)	4,6 (g)	QC (g)	Q2C			
Day	-21 to 1	1							2		8						9		15		1						8	1	1	1	1			
Hours (relative to dosing)		pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	pre	0	0.25	0.5	1								
DOSING																																				
AMG 510 (b)			←==========→																																	
IMAGING ASSESSMENTS																																				
Radiological imaging (CT/MRI) and tumor assessment (c)	X																												X(c)			X(c)	X(c)			
MRI brain (d)	X																																			
PK ASSESSMENTS																																				
AMG 510 PK (e)		X		X	X	X	X	X	X	X		X		X	X	X	X	X	X	X				X		X	X	X						X		
BIOMARKER SAMPLES																																				
Plasma ctDNA (j)		X										X												X								X		X		
Cell pellet from plasma		X										X												X										X		
Serum		X										X												X								X		X		
PB Paxgene RNA(i)		X										X												X								X		X		
BIOMARKER DEVELOPMENT																																				
Tumor biopsy or Archived tumor tissue (FFPE) for solid tumors [f]	X																																	X(f)		

Footnotes defined on next page of the table

(a) A set of triplicate ECGs must be performed at screening; all ECGs will be triplicates with each tracing 30 seconds apart
(b) 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). On cycle 1 day 1, cycle 1 day 8, and cycle 2 day 1, subjects should eat a standard meal at least 2 hours before dosing.
(c) Radiological imaging and tumor assessments are required at screening and every 6 ± 1 weeks cycle 1 day 1 until disease progression, clinical deterioration, intolerance to study medication, withdrawal of consent or start of new anticancer therapy. 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. MRI of the brain is required at screening or if a subject has signs or symptoms suggestive of CNS metastases. Tumor burden assessments will be performed based on RECIST 1.1 guidelines (Appendix D). Radiographic response (CR and PR) requires confirmation by a repeat consecutive assessment at least 4 weeks after the first detection of response.
(d) All subjects with history of brain metastasis 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 can be performed at any time if clinically indicated or per standard of care.
(e) PK 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. PK samples not collected at exact nominal time point will not be considered protocol deviations.
(f) Subjects will provide fresh frozen samples or FFPE samples (collected within 5 years) for *KRAS p.G12C*mutation confirmation or undergo tumor biopsy that enables *KRAS p.G12C*testing prior to starting all other screening procedures; Optional tumor biopsy can be performed at response and at time of progression
(g) Assessments to be performed on day 1 of each cycle. Laboratory Assessments may be performed within 24 hours before Day 1 of each cycle. There are no allowable windows for dosing time points and other assessments during cycle 1 or cycle 2; A window of ± 2 days is allowable after cycle 2
(h) HbA1c should be performed once every 4 cycles
(i) Plasma collection for Paxgene RNA collection required at time of progression
(j) Plasma ctDNA collection required at the beginning of every cycle predose, at response and at time of progression

Table 3. Schedule of Assessment: Part 1 Food Effect Assessment Only

	Treatment																	
Cycle	2 or later																	
Day	1								2								3	
Hours (relative to dosing) (a)	**pre**	**0**	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**pre**	**0**	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**pre**	**0**
DOSING																		
AMG 510 (b)		X								X								X
PK ASSESSMENT																		
AMG 510 PK (c)	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	
RENAL EXCRETION ASSESSMENT																		
Urine (d)								X	X									

(a) Refer to Table 1 for assessments other than for dosing and PK and renal assessments on days 1–3.
(b) Subjects will be administered AMG 510 on day 1 in the fasted state (no food 10 hours before dosing and 3 hours after dosing) and on day 2 in the fed state (dosing with a high fat meal). On day 3, AMG 510 can be administered with or without food per patient discretion.
(c) PK 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. PK samples not collected at exact nominal time point will not be considered protocol deviations.
(d) Urine should be collected from 0–7 hours postdose and 7–24 hours postdose.

Refer to the IPIM, laboratory and site imaging manuals for detailed collection and handling procedures.

7.2 General Study Procedures

A signed and dated IRB/IEC approved informed consent form (ICF) must be obtained prior to performing any study specific procedures, including discontinuing standard therapy for observing study specific washout periods.

Subjects will be seen in the clinic for study evaluations. When ECGs, vital signs, and invasive procedures like blood or biopsy sampling occur on the same visit, ECGs and vital signs should be collected prior to performing any invasive procedures.

Blood samples for biomarker and PK assessments should be drawn from a peripheral vein and not from a central venous catheter. The study specific lab manual will provide additional detail on lab sampling and handling requirements.

Study procedures should be performed and samples obtained at the time points stipulated in the Schedules of Assessments (Table 2 through Table 3). Acceptable deviation windows for study procedures are listed below:

- ECGs, biomarker blood draws, safety labs, vital signs (incl. pulse oximetry):
  - ± 5 minute window (for time points of 0.25 hr and 0.5 hr postdose), ± 15 minute window (all other time points)

Acceptable deviation windows for study visits are listed below:

- Visits during treatment ± 1 day
- SFU: + 7 days
- LTFU: ± 2 weeks for remote survival follow-up

Furthermore, start of a treatment can be delayed for administrative/logistical reasons for up to 7 days to allow for appropriate scheduling after discussion with and final approval by sponsor.

Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the eCRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits. Every effort should be taken to collect all biomarker and PK samples as described in the schedule of assessments. However, if sample processing/shipment on a weekend/holiday is not logistically feasible for a site, this needs to be documented and will not be considered a deviation from the protocol.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

Table 4. List of Analytes

Local Laboratory				Central Laboratory
Chemistry	**Hematology**	**Coagulation**	**Urinalysis**	**Central Lab**
Sodium Potassium Chloride Bicarbonate (HCO3) Total protein Albumin Calcium Magnesium Phosphorous Glucose Blood urea nitrogen [3]Urea Creatinine Total creatine kinase Total bilirubin Direct bilirubin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Serum or Urine Pregnancy Hepatitis B surface antigen Hepatitis C antibody HIV[1]	Hemoglobin Hematocrit Mean corpuscular volume Platelets RBC White blood cell Differential • Total neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	PT or INR PTT or aPTT Fibrinogen D-Dimer	Specific gravity pH Blood Protein Glucose Bilirubin Microscopic exam (performed at the discretion of the Investigator)	PK sampling Plasma ctDNA Plasma cell pellet Serum PB Paxgene RNA antibody Tumor biopsy[2]

[1]Hepatitis B surface antigen, Hepatitis C antibody, PCR for Hepatitis C RNA (if Hepatitis C antibody is positive), and HIV assessments are recommended.
[2]Archived tumor tissue acceptable in Part 1 (Dose Escalation) only
[3]Urea collection is acceptable in absence of BUN

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

7.2.1 Screening

After written consent has been obtained, subjects will be screened in order to assess eligibility for study participation. All screening procedures must be performed within 21 days prior to start of investigational product administration, unless otherwise noted. The ICF may be signed earlier than 21 days prior to start of investigational product in case of washout times that have to be observed to meet eligibility criteria.

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 21-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 each 21-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 Assessments (Table 2 through Table 3). Assessments that were performed as standard of care prior to signature of informed consent, but within 21 days 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.

- confirmation that the ICF has been signed
- demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness
- subjects can be enrolled in the dose exploration based on archived tumor tissue (FFPE) or a pre-treatment biopsy if the archived tissue is not available. Positivity of the *KRAS p.G12C* mutation will be determined by each institutions local or central test (Section 7.4)
- subjects in the dose expansion will provide an archived tumor tissue (FFPE) or pre-treatment tumor biopsy if the archived tumor is not available and/or screening/pre-treatment plasma sample to confirm *KRAS p.G12C* mutation prior to enrollment
    - the tumor tissue samples will be sent to the central lab to determine *KRAS p.G12C* mutation positivity prior to enrollment as explained in Section 7.4
- medical history (including surgical history)
- physical examination (including neurological exam)
- ECOG performance status

- height and weight
- vital signs (ie, blood pressure, heart rate, respiratory rate, temperature)
- pulse oximetry
- ECG triplicate measurement
- radiological assessment must include CT/MRI of the chest, abdomen and pelvis, as well as assessment of all other known sites of disease
- All subjects with history of brain metastasis must have MRI/CT of the brain performed within 28 days prior to enrollment
- laboratory assessments: hematology, chemistry, coagulation, urinalysis, serum pregnancy test (females only and not required if surgically sterile or ≥ 2 years postmenopausal), hepatitis serology
- HIV test
- biomarker assessments:
  - plasma ctDNA, plasma cell pellet, serum and peripheral blood paxgene RNA
- disease assessments:
  - for all subjects: Clinical tumor and radiographic assessment (CT/MRI) at screening and repeated at week 6, week 12, and every 6 weeks untill EOT
- serious adverse event reporting
- documentation of concomitant medication

Re-Screening:

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

Re-screened subjects must be documented as screen failed in the subject's medical record and subsequently documented as re-screened. Subjects will retain the same subject identification number assigned at the time of initial screening. Once the subject is recorded as re-screened, a new 21-day screening window will begin. The following assessments do not have to be repeated during re-screening, 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.

Any other assessments do not need to be repeated if they were performed within 21 days prior to start of treatment with AMG 510.

7.2.2 Treatment

Treatment begins on Day 1 when the first investigational product is administered to a subject.

During clinic visit days all protocol-required predose assessments have to be performed prior to administration of AMG 510.

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 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.

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 2 through Table 3):

- physical examination
- ECOG performance status
- weight
- vital signs (ie, blood pressure, heart rate, respiratory rate, temperature)
- pulse oximetry
- ECG triplicate measurement
- laboratory assessments: hematology, chemistry, coagulation, urinalysis, urine/serum pregnancy test (females only and not required if surgically sterile or ≥ 2 years postmenopausal)
- AMG 510 PK sample collection
- biomarker assessments:
  - plasma ctDNA, plasma cell pellet, serum and peripheral blood paxgene RNA
- serious adverse event reporting
- disease assessments:

clinical tumor and radiographic assessment (CT/MRI) at screening and repeated at week 6, week 12, and every 6 weeks until EOT

- adverse event reporting
- disease-related event reporting

- documentation of concomitant medication
- urine collection (food effect assessment only)

All other assessments should be performed as per the schedule of assessments applicable to the actual cycle

7.2.3 Safety Follow-up Visit

The SFU visit should occur approximately 30 (+7) days after the last dose of AMG 510. Every effort should be made to conduct this visit for all subjects enrolled into the study, including subjects who withdraw from treatment early. The following procedures will be completed during the SFU visit as designated in the Schedules of Assessments (Table 2).

- physical examination
- ECOG performance status
- weight
- vital signs (ie, blood pressure, heart rate, respiratory rate, temperature)
- pulse oximetry
- ECG triplicate measurement
- serious adverse event reporting
- adverse event reporting
- documentation of concomitant medications

7.2.4 Long-term Follow-up

Following the SFU visit, there will be a LTFU period for clinical evaluation of disease status and survival. Subjects will be followed via telephone every 12 weeks (± 2 weeks) for assessment of survival and documentation of anti-cancer treatment. Subjects will be followed for a maximum of 2 years from the first dose of AMG 510, or until subject death, whichever occurs first.

Subjects will allow Amgen continued access to medical records so that information related to subjects' health condition, including disease status and survival, may be obtained.

7.2.5 End of Study Visit

End of study is defined as the date of the final study visit (eg, LTFU) when assessments and/or procedures are performed.

7.2.6 Pharmacokinetic Blood Sampling

For pharmacokinetic assessment blood samples for quantitative determination of AMG 510, will be collected at time points specified in the Schedule of Assessments (Section 7.1). Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

7.2.7 Urine Collection

On day 1 of the cycle in which the food effect assessment is conducted, urine will be collected for the following time periods: (1) 0–6 hours post-dose, and (2) 6–24 hours post-dose.

7.2.8 High-fat Meal

For the food effect assessment, the clinical site will provide standardized high-fat meal as described in the Schedule of Assessment (Table 3). A standard high-fat meal (approximately 50% of the total caloric content of the meal) and high calorie (approximately 800 to 1000 calories) meal will be used as a test meal. The test meal should derive approximately 150, 250 and 500 to 600 calories from protein, carbohydrate and fat, respectively. An example test meal would be 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. Substitutions in this meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. Further details of the high fat meal will be recorded in subject medical record and eCRF.

7.3 Radiological Imaging Assessment

The extent of disease will be evaluated by contrast-enhanced MRI/CT according to RECIST 1.1 (Appendix D). All radiological imaging will be performed as indicated in the Site Imaging Manual provided by the central imaging core laboratory. Organ-specific imaging protocols or existing diagnostic guidelines should be followed whenever possible to evaluate the full extent of the disease appropriately. In order to reduce radiation exposure for subjects, low dose CT or MRI should be applied whenever possible. MRI/CT scans should be performed with contiguous slices thickness of ≤ 5 mm according to the Site Imaging Manual.

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. The same modality, field strength and contrast used at screening should be used for all subsequent assessments. MRI of the brain should be performed if signs or symptoms suggestive of CNS metastases are present.

During treatment, 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 ± 1 weeks until disease progression, clinical deterioration, intolerance of study drug, withdrawal of consent, or start of new anticancer treatment. Imaging may also be performed more frequently if clinically necessitated at the discretion of the managing physician. Radiographic response (Complete Response, Partial Response) requires confirmation by a repeat, consecutive scan at least 4 weeks after the first documentation of response and may be delayed until the next scheduled scan to avoid unnecessary procedures.

All subjects with brain metastasis must have MRI of the brain performed within 28 days prior to first dose of AMG 510. Subsequently, brain scans may be performed at any time if, 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.

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

Determination of disease response for clinical management of subjects will be assessed at the clinical sites per RECIST 1.1. Scans will be submitted to a central imaging core laboratory for archival, response assessment including RECIST 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.

7.4 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess

the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or protocol required therapies.

Amgen may attempt to develop additional test(s) designed to identify subjects most likely to respond positively or negatively to AMG 510, to investigate and further understand the the pharmacodynamic evidence and biological impact of AMG 510 by characterization of changes in levels of gene (DNA or RNA) or protein expression of downstream effectors of EGFR and related markers.

Blood Samples

Blood samples are to be collected for biomarker development as listed in the schedule of assessments. Plasma and/or serum may also be used for DNA, RNA, and protein expression analysis including somatic mutations in order to correlate levels of expression with response.

Tumor Tissues

For archival tumor samples within the first 2 weeks after enrollment, FFPE blocks or unstained slides of tumor tissue must be collected prior to the study is to be sent to the central laboratory along with the corresponding pathology report. Provision of achival tumor samples are allowed prior to enrollment in the Part 1 (Dose Escalation).

Tumor tissue collection following local standard of care procedure is required prior to enrollment in Part 2 (Dose Expansion) and the tissue along with the corresponding pathology report is to be sent to the central lab or affiliate (based on geographical location of the research institution) for testing to establish *KRAS p.G12C* positivity. Collection of tumor tissue following local standard of care procedure for *KRAS p.G12C* testing is not expected to present any additional risk to the health, safety, and welfare of the subject. Subjects will be enrolled in Part 2 of this study based on the result of the *KRAS p.G12C* test. G12C positivity will be determined at the central testing lab with an investigational in-vitro diagnostic device.

The tumor block 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. When the samples of tumor tissues are available, analyses of tumor specific mutations or epigenetic changes may be performed (eg, somatic mutations).

Tumor biopsies are to be collected and pharmacodynamic changes analyzed to determine the effect of the drug on target(s) in the tumor as well as to potentially analyze molecular mechanisms associated with acquired resistance.

Central G12C KRAS Laboratory Methods – Summary

The therascreen® KRAS RGQ PCR Kit from QIAGEN is a real-time qualitative PCR assay performed on the Rotor-Gene Q MDx instrument for the detection of 7 somatic mutations in the human KRAS oncogene using DNA extracted from FFPE tissue. The mutations detected are: G12A, G12D, G12R, G12C, G12S, G12V, G13D. The therascreen® KRAS RGQ PCR Kit is an investigational in vitro diagnostic device that will be used to retrospectively inform subject selection for subjects with *KRAS p.G12C* mutant solid tumors for the Part 1 (Dose Expoloration) and Part 2 (Dose Expansion) of this study.

Patient testing with the therascreen® KRAS RGQ Assay will take place at the NeoGenomics Central Testing Laboratory in Houston, Texas.

The Idylla™ KRAS Mutation Test, for use with the Idylla™ Platform, is an automated real-time PCR based qualitative test for the detection of mutations in KRAS exon 2 (codons 12 and 13), exon 3 (condons 59 and 61), and exon 4 (codons 117 and 146) in DNA extracted from FFPE tissue or plasma. The mutations detected are: G12C, G12R, G12S, G12A, G12D, G12V, G13D, A59T/E/G, Q61K, Q61R/L, Q61H, K117N, A146P/T/V.

Patient testing with the Idylla™ KRAS Mutation Test ® KRAS RGQ Assay will take place at Q2 Solutions central testing laboratories. The Idylla™ KRAS Mutation Test is an investigational in vitro diagnostic device that will be used to inform subject selection for subjects with *KRAS p.G12C* mutant solid tumors for Part 2 (Dose Expansion) of this study.

7.5 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of colorectal cancer, non-small cell lung cancer, pancreatics cancer as well as other solid tumors and/or to identify subjects who may have positive or negative response to AMG 510.

Pharmacogenetic samples are collected for this part of the study. Subjects who consent to this/these analysis/analyses, DNA may be extracted from blood.

7.6 Sample Storage and Destruction

Any blood or tissue samples collected according to the Schedule of Assessments (Table 2) 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 do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the solid tumor cancers (e.g. mCRC, NSCLC, pancreatic cancer) with the dose response and/or prediction of response to AMG 510 , characterize antibody response, 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, biomarker development, 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

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

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, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 2) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, Subjects who have discontinued investigational product and/or 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. The investigator must document the level of follow-up that is agreed to by the subject.

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, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

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

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 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal FromTreatment

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

- subject request
- adverse event
- death
- lost to follow-up
- decision by Sponsor
- non-compliance
- requirement for alternative therapy
- disease progression as defined by RECIST 1.1 criteria (Appendix D) or disease progression accompanied by worsening of symptoms or deterioration of the subject's general condition.
- pregnancy

8.3.2 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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study, or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse 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 eCRF.

For situations when an adverse event or serious adverse event is due to to non-small cell carcinoma of lung, colorectal cancer, or pancreatic adenocarcinoma 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.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI) (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through the end of study are reported using 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),
- Severity and/or toxicity per protocol,
- Assessment of relatedness to investigational product and
- Action taken.

The adverse event grading scale used will be the CTCAE version 4**.** The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to AMG 510. This relationship is indicated by a "yes"

or “no” response to the question: Is there a reasonable possibility that the event may have been caused by AMG 510?

The investigator must assess whether the adverse event is possibly related to any study mandated activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s) and/or procedure (including any screening procedure(s)). This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s)), and/or procedure”?

The investigator is responsible for reviewing laboratory test results and determining 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.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the dosing interval of investigational product are recorded in the subject’s medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator’s knowledge of the event via the Event CRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator’s knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form.

The investigator must assess whether the serious adverse event is possibly related to the investigational product. This relationship is indicated by a “yes” or “no” response to

the question: Is there a reasonable possibility that the event may have been caused by the investigational product(s), and/or other protocol-required therapies? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

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

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local regulatory requirements and procedures.

9.2.1.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge 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 for the purposes of expedited reporting.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking AMG 510 report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur in a female subject through 1 week after the last dose of AMG 510 or in a male subject's female partner through 90 days after the last dose of AMG 510.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through 30 days after the last dose of protocol-required therapies.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoints:

- Safety: subject incidence of dose limiting toxicity (DLTs), treatment-emergent adverse events, treatment-related adverse events, and clinically significant changes in vital signs, physical examinations, electrocardiogram (ECG)s, and clinical laboratory tests

Secondary Endpoints:

- PK parameters of AMG 510 including, but not limited to, maximum observed plasma concentration (C_{max}), time to achieve Cmax (t_{max}), and area under the plasma concentration-time curve (AUC)
- Objective response rate, duration of overall response, progression-free survival, and duration of stable disease measured by CT or MRI and assessed per RECIST 1.1 criteria
- PK parameters of AMG 510 including, but not limited to, C_{max}, t_{max}, and AUC in the fed and fasted state
- AMG 510 exposure/QTc interval relationship

Exploratory Endpoints:

- Pharmacokinetic/pharmacodynamic relationships for safety and/or efficacy endpoints
- AMG 510 excretion in urine
- Characterization of potential metabolites of AMG 510 in plasma and urine, if appropriate
- Quantification of biomarker expression at protein, RNA, and DNA levels, as appropriate
- Potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor samples

10.1.2 Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 510.

The analysis of DLT will be restricted to DLT-evaluable subjects (see Section 3.3 for definition).

The PK Analysis Set will contain all subjects who have received at least 1 dose of the investigational product 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.

10.1.3 Covariates and Subgroups

The relationship of covariates to efficacy endpoints will be explored if appropriate.

Biomarker data may be incorporated in additional exploratory subgroup or multivariate analyses. The analyses of biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoints

10.2 Sample Size Considerations

Part 1 – Dose Exploration: Up to 50 subjects will be enrolled in the dose exploration part of the study. Approximately 30 subjects will be used to estimate the MTD. This sample size is based on practical considerations and is consistent with conventional oncology studies with the objective to estimate the MTD. In order to better estimate the RP2D and to better characterize the safety, efficacy and pharmacodynamics, an additional 20 subjects may be enrolled to one or more dose levels that have been shown to be safe and tolerable from which at least 6 subjects will be evaluated for food effect. With 2 subjects per cohort, there is a 27-70% probability of observing at least one DLT if the true DLT rate is 10-33% and with 4 subjects per cohort, there is a 34-80% probability. With 10 subjects in a cohort, there is a 65-98% probability of observing at least one DLT if the true DLT rate is 10-33%. The sample size of at least 6 subjects for food effect evaluation is based on practical considerations and judged sufficient for the evaluation; no formal calculation was made.

Part 2 – Dose Expansion: Approximately 60 subjects will be enrolled in the dose expansion part of the study, which will be conducted in at least 3 groups.
Group 1: approximately 20 subjects with advanced *KRAS p.G12C*mutant NSCLC.
Group 2: approximately 20 subjects with advanced *KRAS p.G12C* mutant CRC.
Group 3: approximately 20 subjects with advanced *KRAS p.G12C* mutant all other solid tumors. The sample sizes for groups 1 through 3 are based on practical considerations. With 20 subjects in each group, there is a 88% to 99% probability of observing at least 1 adverse event if the true event rate is 10% to 20%. For each group, an exact

80% binomial CI will be provided for ORR. With the 20 subjects in each group and a 20% ORR, the 80% CI would be 9.0% to 36.1%.

10.3 Adaptive Design

The adaptive features of the BLRM design are described in Appendix E.

10.4 Planned Analyses

The following data analyses are planned: (1) the primary analysis after all dose-escalation and dose-expansion subjects had the opportunity to receive up to 6 months of treatment or terminated the study early, and (2) the final analysis after all subjects have ended the study.

10.4.1 Interim Analyses

Safety data will be reviewed on an ongoing basis. Based on accumulating toxicity information, BLRM will be used to make dosing recommendations. In DLRMs, Amgen, in consultation with the site investigators, will review the BLRM recommended dose level and will review all available cumulative data by cohort prior to making dose escalation decisions. As a sensitivity analysis, a one-parameter Continual Reassessment Method (CRM) model may be used to estimate the dose-toxicity relationship to help making dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions.

An interim analysis for efficacy parameters will be conducted after dose escalation is completed.

10.4.2 Dose Level Review Team (DLRT)

After all DLT-evaluable subjects within a cohort have completed the DLT window, a DLRM will be held to review data, monitor safety, and recommend dose change decisions. The review team will be composed of the investigators, Amgen Medical Monitor, Amgen Global Safety Officer or designated safety scientist, Amgen Early Clinical Development Manager, and Biostatistics representative. Additional members may be added as needed (e.g. 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 decision 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 global safety officer or designated safety scientist, and all actively screening and enrolling investigators or their qualified sub-investigator designee. The team may recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), continuation or delay in dosing, repetition or expansion of a cohort, de-escalation to a lower dose, or termination of the study. The Amgen medical monitor and Global Safety Officer or designee 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. All available study data including demographics, medical history, concomitant medications, AEs, electrocardiograms (ECGs), vital signs, laboratory results, and emerging PK or pharmacodynamics data will be reviewed.

The following recommendations will be made by the DLRT:

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

10.4.3 Primary Analysis

The primary analysis will occur when target enrollment is complete and each subject had the opportunity to receive up to 6 months of treatment or terminated the study early.

10.4.4 Final Analysis

A final analysis is planned after all dose-escalation cohorts and dose-expansion subjects 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.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamics and biomarker data by dose, dose schedule, 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. A two-parameter BLRM will be used to estimate the dose-toxicity relationship. See Appendix E for the description of the two-parameter BLRM design.

10.5.2 Primary Endpoint(s)

Safety Endpoints

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 at least 1 dose of AMG 510.

Subject incidence of DLTs will be used to fit the BLRM model to estimate the probability of having a DLT across dose levels.

Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. The number and percentage of subjects reporting adverse events will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.

Tables of fatal adverse events, serious adverse events, and adverse events leading to withdrawal from investigational product or other protocol-required therapies will also be provided.

Clinical Laboratory Tests

Clinical chemistry, hematology, and urinalysis data will be presented and reviewed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided.

Vital Signs

Vital signs data will be presented and reviewed for each subject. Depending on the size and scope of changes, summaries of vital signs data over time and/or changes from baseline over time may be provided.

Electrocardiograms

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

Subjects' maximum change from baseline in QT interval corrected by Fridericia's formula 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 presented, and select parameters of interest may be plotted.

10.5.3 Secondary Endpoint(s)

10.5.3.1 Pharmacokinetics Data Analysis

For AMG 510, pharmacokinetic 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.

10.5.3.1.1 Food Effect Assessment

The food-effect cohort PK parameter estimates will help assess the impact of food on the pharmacokinetics of AMG 510. The geometric means and 90% confidence interval for the ratio of the geometric means (fed state/fasted state) will be estimated using a mixed-effects model. The model will use the log-transformed PK parameters as the dependent variable (or response) and treatment conditions (fed versus fasted) as the independent variable. The median of t_{max} will be compared between fasted and fed conditions as well.

10.5.3.2 Efficacy Endpoint Analyses

The proportion of subjects with an objective response (CR or PR) and disease control (CR, PR or SD>xx months) with corresponding exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) and tabulated for subjects treated at the MTD or RP2D. The efficacy endpoints: progression-free survival, duration of response and duration of stable disease will be presented. A Kaplan-Meier curve may be presented for progression-free survival with estimates for rates and 95% CI at selected weeks. Statistical analyses of efficacy endpoints will be considered exploratory.

10.5.4 Exploratory Endpoints

The following statistical analyses will be considered exploratory and will be performed only when deemed appropriate. Relationships between changes in tumor dynamics and above biomarkers of interest listed as exploratory endpoints will be explored. Changes in expression levels of biomarkers and their relationship to dose may also be explored. Summary statistics over time will be provided and graphical presentations may be used. The relationship between AMG 510 exposure and pharmacodynamics effects and related biomarkers in blood or tumor specimens and/or AMG 510 exposure and clinical outcomes (eg, tumor response) will be also explored if deemed appropriate. Details of analysis will be provided in a supplemental analysis plan for exploratory biomarker analysis.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Study Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any investigational product(s) is/ are administered. A legally acceptable representative is 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.

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. 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 informed consent form 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. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable 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 informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

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 is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for 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.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the 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 date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in strict confidence by the investigator, except as described below.

In compliance with governmental/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 named such individuals to have access to his/her study related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center 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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, the Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB/IEC must be informed of all amendments and give approval. 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.

Amgen reserves the right to terminate the study at any time. 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 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 it is available commercially.

12.2 Study Documentation and Archive

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 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.

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 CRF, informed consent forms, 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 (POR), 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.

12.3 Study Monitoring and Data Collection

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.

The Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the CRFs.

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.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing 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.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same

date with different visit, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 1), the investigator can search publically 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.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

12.6 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should 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 should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should 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 should qualify for authorship, and all those who qualify should be listed.
- Each author should 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 corporate review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 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.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following location:

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

Drug-induced Liver Injury Reporting & 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 Section 6.2 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, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the 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 9.1.2

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 Section 6.2 or who experience AST or ALT elevations > 3 x ULN or 2-fold increase above baseline values for subjects with evaluated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, 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 (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) 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
  - CPK, haptoglobin, LDH, 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 an 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 corresponding CRFs.

Appendix B. Sample Serious Adverse Event Form

AMGEN Study # 20170543 AMG 510	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

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

3. SERIOUS ADVERSE EVENT

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

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? <Device> No✓ Yes✓	<Device> No✓ Yes✓	<Device> No✓ Yes✓	<Device> No✓ Yes✓	Outcome of Event *Resolved Not resolved Fatal Unknown*	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 510	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20170543 AMG 510	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20170543 AMG 510	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

Signature of Investigator or Designee - *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20170543

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 DOB: mm ____ / dd ____ / yyyy ____

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 LMP mm ____ / dd ____ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ____ / dd ____ / yyyy ____ ☐ Unknown ☐ N/A

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: _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20170543

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 Date of Birth:** mm____ / dd____/ yyyy____

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:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix D. Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

Quick Reference

Definitions

- **Measurable Lesions**
  - Measurable Tumor Lesions - Lesions that can be accurately measured in at least 1 dimension with longest diameter ≥ 10 mm in 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 two 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 (tumor lesions with longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis with CT scan slice thickness no greater than 5 mm) and truly non-measurable lesions (ie, blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cysts, and also abdominal masses that are not confirmed and followed by imaging techniques).

Methods of Meseasurement

- **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 IV contrast as well as timing of scanning. CT 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 five (5) lesions per organ and ten (10) 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 case report form (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 < 10mm.
* 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 5mm in the sum of the diameters of target lesions, taking as reference the smallest sum on study, or the appearance of one or more new lesions.
	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD,

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 lesion(s) or/and maintenance of tumor marker level above the normal limits.
* Progressive Disease (PD):	Unequivocal progression of existing non-target lesions and/or appearance of one or more new lesions.[1]

[1]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 one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Evaluation of Objective Response

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
Any	Any	Yes	PD

NE = Not evaluable

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‡
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

‡ "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 CR and PR required

Overall Response First Time Point	Overall Response Second Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[†]
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

[†] 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 the 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 CR, each node must achieve a short axis < 10 mm. For PR, SD and pharmacodynamics, the actual short axis measurement of the nodes is to be included in the sum of diameters.
- Target lesions that become "too small to measure" – While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.
- New lesion – 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. 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.

- 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 even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation Measurement / Duration of Response

- **Response Confirmation -** In non-randomized trials where response is the primary endpoint, confirmation of PR and CR 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 progressive disease 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.

Appendix E. Two-Parameter BLRM Design

A two-parameter Bayesian logistic regression model (BLRM, Neuenschwander et al, 2008) is used to guide dose escalation. The MTD target Toxicity Probability Interval (TPI) for DLT is (0.20, 0.33) and a TPI of (0.33, 1.00) is defined as excessive. The design seeks to identify a dose most likely to have a DLT rate in the target TPI, but with overdose control that limits the possibility the dose has an excessive DLT rate (Babb et al, 1998). The probability of a DLT at dose level d_i is assumed to follow a Bernoulli distribution with probability p_i where the logit of p_i increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

$$\log [p_i / (1-p_i)] = \text{logit}(p_i) = \log[a] + \exp(\log[b]) \log (d_i / d_{ref})$$

where a and b are random variables and d_{ref} is one of the planned dose selected as the reference dose.

A bi-variate normal prior distribution (Neuenschwander et al, 2008) was selected for theta = (log a, log b) where the probability that the true DLT rate is ≤ 0.40 at 180 milligrams (mg) is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose (720 mg) is 0.05. Additionally, the prior is such that p_i is approximately 0.05 for the 180 mg dose and 0.25 for the reference dose.

The operating characteristics of the two-parameter BLRM design were evaluated via simulation. The cohort size was fixed to 2 or 4 subjects. The initial dose level is 180 mg and subsequent doses were selected based on the following rules:

- After each cohort, the next dose is the one with the highest probability of the target TPI, but with a less than 0.25 probability of an excessive TPI.
- Escalation to a dose level that is greater than 2x the current dose level is not allowed.

Dose escalation was stopped given 1 or more of the following conditions:

- There have been at least 6 subjects treated at the dose recommended by the model.
- A maximum number of 30 subjects are evaluated.

Operating characteristics are described below.

Operating characteristics

A total of 4 planned dose levels (unit: mg) were considered: 180, 360, 720 and 960. Two intermediate dose levels were also considered: 270 and 540 mg. The design was evaluated for 4 possible dose-response scenarios: Low MTD, Mid MTD, High MTD and

a scenario where none of the planned dose levels are tolerable.Table 5 shows the dose level and true probability of DLT for each scenario used in the simulated studies estimating the MTD. Table 6 reports the operating characteristics from 1000 simulated studies estimating the MTD when the target TPI is (0.20, 0.33). The rate of MTD selected and the number of subjects assigned to each dose level are presented in Table 7

Table 5. True Probability of DLT by Scenario for Simulated Studies Estimating MTD

Dose Level	180	270	360	540	720	960
MTD Scenario						
High	0.01	0.01	0.05	0.15	0.25	0.33
Mid	0.05	0.15	0.25	0.33	0.43	0.53
Low	0.15	0.25	0.33	0.43	0.53	0.63
No tolerable dose levels	0.35	0.43	0.50	0.58	0.65	0.73

DLT = dose-limiting toxicity; MTD = maximum tolerated dose

Table 6. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD When the Target TPI is (0.20, 0.33)

MTD Scenario	High		Mid		Low		No tolerable dose levels	
Subjects per cohort	4	2	4	2	4	2	4	2
Number of Subjects Median (IQR)	20 (16 to 24)	12 (12 to 14)	20 (16 to 24)	12 (10 to 14)	16 (12 to 20)	10 (2 to 14)	8 (4 to 12)	2 (2 to 8)
Number of DLTs Median (IQR)	2 (2 to 4)	2 (1 to 2)	4 (3 to 5)	3 (2 to 3)	4 (3 to 6)	2 (1 to 4)	3 (2 to 4)	2 (1 to 3)
Proportion of DLT (%) Median (IQR)	12.5 (10 to 17)	14.3 (8 to 19)	25.0 (19 to 25)	25.0 (19 to 35)	26.7 (25 to 37)	37.5 (25 to 50)	50.0 (37 to 50)	50.0 (43 to 50)
Percentage of studies recommending dose with DLT probability of:								
≤ 10%	4.6	9.2	11.2	25.9	29.7*	53.6*	82.3*	89.3*
> 10% and ≤ 20%	47.2	55.6	4.6	2.0	10.3	0.9	NA	NA
> 20% and ≤ 33%	48.2	35.2	78.2	64.3	47.5	30.3	NA	NA
> 33%	NA	NA	6.0	7.8	12.5	15.2	17.7	10.7
Probability of identifying MTD to have 15% to 33% DLT probability	95.4	90.8	82.8	66.3	57.8	31.2	NA	NA

DLT = dose-limiting toxicity; IQR = interquartile range; MTD = maximum tolerated dose; TPI = toxicity probability interval; NA=not applicable
*In the low MTD scenario and the scenario where all planned dose levels are intolerable, this represents the percent of studies declaring all planned dose levels as not tolerable.

Table 7. Rate of MTD Selected and Number of Subjects Assigned at Each Dose Level by Scenario

MTD Scenario	High		Mid		Low		No tolerable dose levels	
Number of Subjects Per Cohort	4	2	4	2	4	2	4	2
Rate of MTD selected at each dose level (%):								
Below lowest dose	0.2	2.6	8.1	25.0	29.7	53.6	82.3	89.3
180 mg	0.1	0.0	3.1	0.9	10.3	0.9	9.2	0.9
270 mg	0.0	0.0	4.6	2.0	9.0	2.2	3.2	1.0
360 mg	4.3	6.6	43.8	31.3	38.5	28.1	4.7	7.4
540 mg	47.2	55.6	34.4	33.0	10.8	14.3	0.5	1.4
720 mg	44.3	33.2	5.2	7.8	1.6	0.9	0.1	0.0
960 mg	3.9	2.0	0.8	0.0	0.1	0.0	0.0	0.0
Average number of subjects at each dose level								
180 mg	4.1	2.0	4.7	2.3	5.3	2.4	5.1	2.4
270 mg	0.2	0.2	1.6	0.8	2.1	0.9	1.4	0.5
360 mg	4.3	2.5	6.0	3.5	5.1	3.1	1.6	1.7
540 mg	5.3	4.3	4.7	3.2	2.6	1.9	0.3	0.6
720 mg	5.6	3.3	1.8	1.4	0.7	0.5	0.1	0.1
960 mg	0.5	0.2	0.2	0.0	0.1	0.0	0.0	0.0

MTD = maximum tolerated dose.

Operating Characteristics for Standard 3+3 Design

As a comparison, the operating characteristics from 1000 simulated studies estimating the MTD when using a standard 3+3 design are reported in Table 8.

Table 8. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD Using a 3+3 Design

MTD Scenario	High	Mid	Low	No tolerable dose levels
Number of Subjects	15	12	12	6
Median (IQR)	(12 to 18)	(12 to 15)	(9 to 13)	(3 to 12)
Number of DLTs	2	3	3	3
Median (IQR)	(2 to 3)	(2 to 4)	(2 to 4)	(2 to 3)
Proportion of DLT (%)	16.7	23.8	26.7	33.3
Median (IQR)	(11 to 20)	(20 to 27)	(22 to 33)	(33 to 67)
Percentage of studies recommending dose with DLT probability of:				
≤ 10%	44.7	43.5	19.4*	65.9*
> 10% and ≤ 20%	0.0	0.0	47.4	NA
> 20% and ≤ 33%	55.3	43.3	29.5	NA
> 33%	NA	13.2	3.7	34.1
Probability of identifying MTD to have 15% to 33% DLT probability	55.3	43.3	76.9	NA

DLT = dose-limiting toxicity; IQR = interquartile range; MTD = maximum tolerated dose; NA=not applicable
*In the low MTD scenario and the scenario where all planned dose levels are intolerable, this represents the percent of studies declaring all planned dose levels as not tolerable.

Title: A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 Monotherapy in Subjects With Advanced Solid Tumors With *KRAS p.G12C* Mutation and AMG 510 Combination Therapy in Subjects With Advanced NSCLC With *KRAS p.G12C* Mutation

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[redacted]

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Amendment 1 Date: 12 July 2018

Amendment 2 Date: 13 March 2019

Superseding Amendment 2 Date: 28 March 2019

Superseding Amendment 2 Date: 2 April 2019

Amendment 3 Date: 22 May 2019

Confidentiality Notice

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Investigator's Agreement

I have read the attached protocol entitled "A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 Monotherapy in Subjects With Advanced Solid Tumors With *KRAS p.G12C* Mutation and AMG 510 Combination Therapy in Subjects With Advanced NSCLC With *KRAS p.G12C* Mutation", dated **22 May 2019**, 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) 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)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one 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)

Protocol Synopsis

Title: A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 Monotherapy in Subjects with Advanced Solid Tumors With *KRAS p.G12C* Mutation and AMG 510 Combination Therapy in Subjects With Advanced NSCLC With *KRAS p.G12C* Mutation

Study Phase: 1/2

Indication: *KRAS p.G12C* mutant advanced solid tumors

Objectives

Phase 1 (Monotherapy - Parts 1a, 1b, and 2a)

- **Primary Objectives:**
  - To evaluate the safety and tolerability of AMG 510 in adult subjects with *KRAS p.G12C* mutant advanced solid tumors
  - To estimate the maximum tolerated dose (MTD) and/or a recommended phase 2 dose (RP2D) in adult subjects with *KRAS p.G12C* mutant advanced solid tumors
- **Secondary Objectives:**
  - To characterize the pharmacokinetics (PK) of AMG 510 following administration as an oral tablet formulation
  - To evaluate tumor response assessed by response evaluation criteria in advanced solid tumors (**RECIST**) 1.1 of AMG 510 as monotherapy in advanced solid tumors with *KRAS p.G12C* mutation
  - To evaluate the effect of food on the oral PK of AMG 510
  - To evaluate the relationship between changes in corrected QT interval (QTc) and AMG 510 exposure

[redacted]

Phase 2 (AMG 510 Monotherapy):

- **Primary Objective**
  - To evaluate tumor objective response rate (ORR), assessed by **RECIST** 1.1 criteria, of AMG 510 as monotherapy in subjects with *KRAS p.G12C* muta**nt** advanced solid tumors (NSCLC, colorectal cancer [CRC], and other tumor types).

- **Secondary Objectives**
  - To evaluate other measures of AMG 510 efficacy as monotherapy in subjects with *KRAS p.G12C* muta**nt** advanced solid tumors by **RECIST** 1.1 (NSCLC, CRC, and other tumor types).
    - Duration of response (DOR)
    - Disease control rate (DCR)
    - **Time to response (TTR)**
    - Progression-free survival (PFS)
    - Overall survival (OS)
    - PFS rate at 6 months and 12 months
    - OS rate at 12 months
  - To evaluate the safety and tolerability of AMG 510 in adult subjects with *KRAS p.G12C* mutant advanced solid tumors (NSCLC, CRC, and other tumor types).
  - To evaluate the PK of AMG 510 following administration as an oral tablet formulation

Hypotheses:

The following hypotheses will be tested with this clinical protocol:

Phase 1 (monotherapy [redacted]:

- At least 1 dose level of AMG 510, in repeat oral administrations, will achieve acceptable safety and tolerability in subjects with *KRAS p.G12C* mutant advanced solid tumors in [redacted] monotherapy [redacted]
- A favorable PK profile will be achieved with AMG 510 administered orally as monotherapy [redacted]
- Responses will be observed at a monotherapy dose level that achieves acceptable safety and tolerability.

Phase 2 (AMG 510 monotherapy):

- A clinically relevant ORR will be observed in each tumor type (NSCLC, CRC or other tumor type) at a dose level that demonstrates acceptable safety and tolerability

Endpoints

Phase 1:

Monotherapy (Parts 1a, 1b, and 2a):

- **Primary Endpoints:**
  - Safety: subject incidence of treatment-emergent adverse events, treatment-related adverse events, and clinically significant changes in vital signs, physical examinations, electrocardiogram**s** (ECGs), and clinical laboratory tests
  - Subject incidence of dose limiting toxicity (DLT)

- **Secondary Endpoints:**
  - PK parameters of AMG 510 including, but not limited to, maximum plasma concentration (C_{max}), time to achieve Cmax (t_{max}), and area under the plasma concentration-time curve (AUC)
  - ORR, DOR, DCR, **PFS**, duration of stable disease**, and TTR** measured by CT or MRI and assessed per **RECIST** 1.1. Response will be assessed by independent radiologic review. Complete response and PR require confirmatory CT or MRI repeat assessment 4 weeks after the first detection of response.
  - PK parameters of AMG 510 including, but not limited to, C_{max}, t_{max}, and AUC in the fed and fasted states for the food effect assessment
  - AMG 510 exposure/QTc interval relationship

[redacted]

Phase 2 (AMG 510 Monotherapy):

- **Primary Endpoint**
  - Objective response rate (ORR = complete response [CR] + partial response [PR]), assessed per **RECIST** 1.1. Response will be assessed by independent radiologic review. Complete response and PR require confirmatory CT or MRI repeat assessment 4 weeks after the first detection of response.
- **Secondary Endpoints**
  - Duration of response - defined as time from first evidence of confirmed PR or CR to disease progression or death due to any cause, whichever occurs first. Subjects without a duration ending event will be censored at their last evaluable disease assessment date. Progression will be based on an independent radiologic assessment of disease response per **RECIST** 1.1
  - Disease control rate defined as CR + PR + stable disease rate measured as described for ORR
  - Progression-free survival - defined as time from first dose of AMG 510 until disease progression or death from any cause, whichever occurs first. Subjects who do not progress or die will be censored at their last evaluable disease assessment date. Progression will be on an independent radiologic assessment of disease response per **RECIST** 1.1.
  - Overall survival - defined as time from first dose of AMG 510 until death from any cause. Subjects who do not die will be censored at the date of last contact.
  - Progression-free survival rate at 6 months and 12 months
  - Overall survival rate at 12 months

- Incidence and severity of adverse events
- Pharmacokinteics parameters of AMG 510 including, but not limited to, C_{max}, t_{max}, and AUC.
- **Time to response - defined as time from first dose of AMG 510 until the first evidence of confirmed PR or CR**

Study Design: This is a phase 1/2 multicenter, non-randomized, open-label study of orally administered AMG 510 in subjects with *KRAS p.G12C* mutant advanced solid tumors. The study will be conducted at approximately 100 sites globally.

Phase 1 is a first in human (FIH) dose exploration/expansion study to define the MTD or RP2D, safety, tolerability, PK and pharmacodynamics of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors **(Phase 1, Part 1a, 1b, and 2a)** and [redacted] The phase 1 portion of the study will be conducted in 2 parts: part 1 – Dose Exploration and part 2 – Dose Expansion. Part 1 is aimed at evaluating the safety, tolerability, PK, and pharmacodynamics and determining the MTD of repeat daily (QD) (or twice daily [BID]) dosing for AMG 510 monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors using a Bayesian Logistics Regression Model (BLRM) design and [redacted] The dose expansion part of the study (part 2) can open once the MTD and/or a RP2D has been determined in part 1. The DLT evaluation period will be 21 days.

Phase 2 is a multicenter, non-randomized, open-label, phase 2 study to evaluate efficacy and safety/tolerability of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors (NSCLC, CRC, and other tumors).

Administration of AMG 510 may continue **until subject has confirmed disease progression, or discontinues from the treatment for reasons listed in Section 8.3.1.**

Phase 1:

Dose Exploration – Part 1

Part 1a Monotherapy Cohorts (Once Daily Dosing – QD):

Dose exploration monotherapy cohorts will estimate the MTD, and evaluate the safety, tolerability, PK, and pharmacodynamics of different doses of AMG 510 administered orally once daily in subjects with KRAS p.G12C mutant advanced solid tumors. Enrollment into the dose exploration cohorts may be from any eligible solid tumor type. Dose escalation will begin with 2-4 subjects treated at the lowest planned dose level of 180 mg. Dose escalation will follow the planned schedule with 2-4 subjects treated in each cohort. If no DLT is observed, dose escalation will continue to the next planned dose cohort as per Table 1. **In addition to the dose levels outlined in Table 1, intermediate doses of 270 mg and 540 mg may be explored.** Upon escalation to the next planned dose cohort, sentinel dosing will apply. There will be a 2-day window between the first subject dosed and subsequent subjects. Once a subject experiences a DLT, dosing for subsequent cohorts will be recommended using the dose level recommendation from the BLRM. The decision to advance to the next dose level will be recommended by the Dose Level Review Team (DLRT) using the dose level recommendation from BLRM, as appropriate, and by evaluating available safety data, laboratory, and PK information.

Intra-subject dose escalations are allowed on this study. Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle if the next dose cohort is deemed safe at that time by the DLRT and after consultation with the sponsor if:

- no DLT has been reported for this subject during or after completion of the DLT period
- the subject has not experienced any ≥ grade 2 adverse events (deemed treatment related by the investigator) during treatment

Subjects who proceed to a higher dose level will be required to have back to back clinic visits on day 1 and day 2 at the beginning of the cycle with the higher dose. The safety assessments of chemistry and urinalysis will be performed on day 1 and day 2. A repeat of PK sample collection will be performed as on cycle 1 day 1 and cycle 1 day 2, regardless of actual study cycle.

Subjects who do not proceed to a higher dose may continue to receive additional cycles at the original dose.

Dose exploration will continue until any of the following events.

- the highest planned dose level is determined to be safe and tolerable (minimum of 6 DLT-evaluable subjects)
- the MTD is identified, BLRM recommends a dose level which already has 6 DLT-evaluable subjects

Additional subjects (20 to 40) may be enrolled in one or more **monotherapy** dose levels that have been shown to be safe and tolerable; defined as backfill enrollment. This backfill enrollment will be done to better estimate the RP2D and better characterize the safety, efficacy, PK, and pharmacodynamics for AMG 510 **monotherapy** and may be concurrent with dose escalation to identify the MTD. Additionally, food effect **assessment** will be conducted in at least 6 subjects from backfill enrollment in cycle 2 or later.

Part 1b Monotherapy Cohorts (Twice Daily Dosing – BID):

A BID dosing schedule for AMG 510 may be investigated as a dose modification strategy to potentially optimize AMG 510 activity. The initiation of the BID dosing schedule will be based upon the totality of the data available from Part 1a **and food effect assessment**. Approximately 12 subjects may be enrolled in 2 cohorts of 3 to 6 subjects per cohort.

[redacted]

Dose Expansion – Part 2

Upon completing the dose exploration part of the study and depending on data obtained, dose expansion may proceed with 2 groups consisting of subjects with *KRAS p.G12C* mutant solid tumors:

- Part 2a subjects with *KRAS p.G12C* mutant advanced NSCLC, CRC, or other tumor types administered AMG 510 monotherapy once daily (total approximately n = 20, maximum n = 60)**.**
- [redacted]

Dose expansion in these 2 groups may be done concurrently.

Transition From Monotherapy Phase 1 (Part 2a) Dose Expansion to Phase 2:

After a **minimum** of 20 subjects have been enrolled to the initial estimated monotherapy RP2D (including subjects enrolled to the RP2D in either the dose exploration or the dose expansion parts of the study) and have completed the 21-day DLT period, the DLRT will review all available safety, laboratory, PK, and efficacy (physician assessment) data (including all previous data from the dose expansion and backfill cohorts)**. Antitumor activity will also be monitored in terms of ORR by tumor types (NSCLC, CRC). Futility and efficacy thresholds will be calculated using Bayesian posterior probability approach based on the cumulative efficacy data and it will serve as a guidance to the DLRT. DLRT will** make a recommendation as to whether to proceed to the phase 2 monotherapy part of the study. The DLRT may also recommend that additional subjects be enrolled at this estimated monotherapy RP2D or that a dose reduction or alternate dosing regimen be explored before proceeding to phase 2. After this first review has been conducted, if a decision is made to continue to obtain additional data at the initial estimated RP2D prior to proceeding to phase 2, the intervals for subsequent reviews will be determined by the DLRT but should occur within a maximum of 20 additional subjects enrolled and dosed for 21 days. The maximum number of subjects that may be enrolled to the initial estimated RP2D in the monotherapy dose expansion group, without confirmation of this dose for phase 2, will not exceed 60. If another dose (or schedule) needs to be explored, additional subjects on that dose (or schedule), up to a total of 60, may be enrolled. **Whenever DLRT will review the data, the futility and efficacy thresholds will be calculated based on all the cumulative efficacy data to provide the guidance.**

Phase 2:

This is a multicenter, non-randomized, open-label, phase 2 study to evaluate efficacy and safety/tolerability of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors (NSCLC, CRC, and other tumors). The dose (and schedule) administered in phase 2 will be that confirmed to be the RP2D from combined analyses of phase 1 part 1 and 2. **Approximately 200 subjects (at least 105 for NSCLC and 60 CRC) will be enrolled. The timing to start enrollment into each tumor type will be communicated to the sites and may be gated based on Amgen's internal decision based on several factors (ie, efficacy and availability of the drug supply).** Tumor response will be evaluated employing **RECIST** 1.1 based on contrast enhanced computed tomography (CT)/magnetic resonance imaging (MRI) with assessments conducted by an independent radiological central laboratory. Interim safety reviews will be conducted after 30, 50, 70, and 100 subjects have been enrolled and treated with AMG 510 for at least 21 days (enrollment will not be held for completion of these safety reviews). Interim futility analyses will be conducted as described in Section 10.4.1.3.2. **The primary analysis for the study will occur when there are 105 evaluable NSCLC subjects or 60 evaluable CRC subjects in the phase 2 ORR analysis set (Section 10.1.2.5), whichever occurs first.**

Sample Size:

Phase 1:

It is anticipated that up to 158 subjects will be enrolled in the phase 1 part of the study. **No more than 92 subjects will be enrolled in part 1 (dose exploration) cohorts and up to 66 subjects will be enrolled in part 2 (dose expansion) cohorts.**

Part 1 – Dose Exploration:

Part 1a

Approximately 30 subjects will be needed to estimate the AMG 510 monotherapy MTD in part 1a. An additional 20 to 40 subjects may be enrolled by backfill enrollment and receive AMG 510 monotherapy (part 1a) from which at least 6 subjects will be evaluated for food effect.

Part 1b

Approximately 12 subjects may be enrolled in 2 cohorts of 3 to 6 subjects per cohort.

[redacted]

Phase 2:

In phase 2, it is anticipated that approximately **200** subjects **(at least 105 subjects with NSCLC and 60 subjects with CRC)** will be enrolled. **Actual enrollment for each tumor type (NSCLC, CRC) will be based on DLRT recommendations and Amgen's internal decision.**

The rationale for the number of subjects is provided in Section 10.2.

Summary of Subject Eligibility Criteria:

Adult subjects (≥ 18 years old) with advanced solid tumors will be eligible for this study. Enrollment will be restricted to subjects with *KRAS p.G12C* mutant solid tumors as assessed by molecular testing of tumor biopsy specimens. [redacted]

Once consented to the study, subjects will provide a medical history and undergo screening safety tests to confirm all eligibility requirements of the study have been met. [redacted]

Amgen Investigational Product Dosage and Administration:

AMG 510 for phase 1 will be manufactured both by Amgen Inc. and Patheon. AMG 510 for phase 2 will be manufactured by Patheon. AMG 510 for both phases will be packaged and distributed by Amgen Inc., using Amgen clinical study drug distribution procedures.

AMG 510 will be administered orally once or twice daily [BID]), depending on what phase and/or cohort of the study that the subject is enrolled. No drug holidays are allowed.

Non-Amgen Investigational Product Dosage and Administration (Phase 1 Parts 1c and 2c Only):

[redacted]

Procedures:

After written informed consent has been obtained, all screening tests and procedures will be performed within 2**8** days of administration of the first dose of AMG 510 (day 1),. Subjects will be seen in clinic where critical clinical safety and study evaluations will be performed including physical examination, vital signs, clinical laboratory tests, **imaging assessments,** ECGs, PK, and biomarker sample collections. **Patient-reported outcomes will also be collected.**

Statistical Considerations:

In the phase 1 dose exploration part of the study, the DLRT will review the safety data after each cohort and make a decision on the next dose level to be explored for the estimate of RP2D/MTD based on a BLRM design. Before making a recommendation to proceed to the phase 2 part of the study, the DLRT will review all available safety, laboratory, PK, and efficacy after a minimum of 20 subjects have been enrolled to the initial estimated monotherapy RP2D (including subjects enrolled to the RP2D in either the dose exploration or the dose expansion); all previous data from the dose expansion and backfill cohorts will also be reviewed. **Antitumor activity will also be monitored in terms of ORR by tumor types (NSCLC, CRC). Whenever DLRT will review the data, ORR futility and efficacy thresholds by tumor type will be calculated based on the cumulative efficacy data using Bayesian posterior probability and the thresholds will serve as a guidance to the DLRT.** The DLRT may review additional subjects at a given RP2D (not to exceed 60 subjects).

In the phase 2 part of the study, a data review team (DRT), internal to Amgen but external to the study team, will assess safety after approximately 30, 50, 70, and 100 subjects become evaluable. The DRT will also oversee futility analyses based on ORR that will be performed by tumor type when **25** subjects become evaluable **and every 10 subjects afterwards** for NSCLC and when **20**subjects become evaluable **and every 10 subjects afterwards** for **CRC**. Interim futility analyses will be conducted as described in Section 10.4.1.3.2.

The primary analysis will occur when **either 105** NSCLC subjects or **60** CRC subjects **enrolled in the phase 2 are treated at the monotherapy RP2D and become evaluable**, whichever occurs first**. T**his analysis will **only** include phase 2 subjects treated at the monotherapy RP2D.

Efficacy and safety analyses will be summarized overall and by tumor type. The percentage of subjects with an overall response (OR) will be summarized along with a Clopper-Pearson exact confidence interval. DOR will be summarized with Kaplan-Meier quartiles and rates for select durations (eg, > 3, > 6, > 9, > 12 months). Disease control will be analyzed by the same methods used to analyze OR. Overall survival and PFS will be summarized with Kaplan-Meier curves, quartiles, and rates for select timepoints (eg, 6 and 12 months).

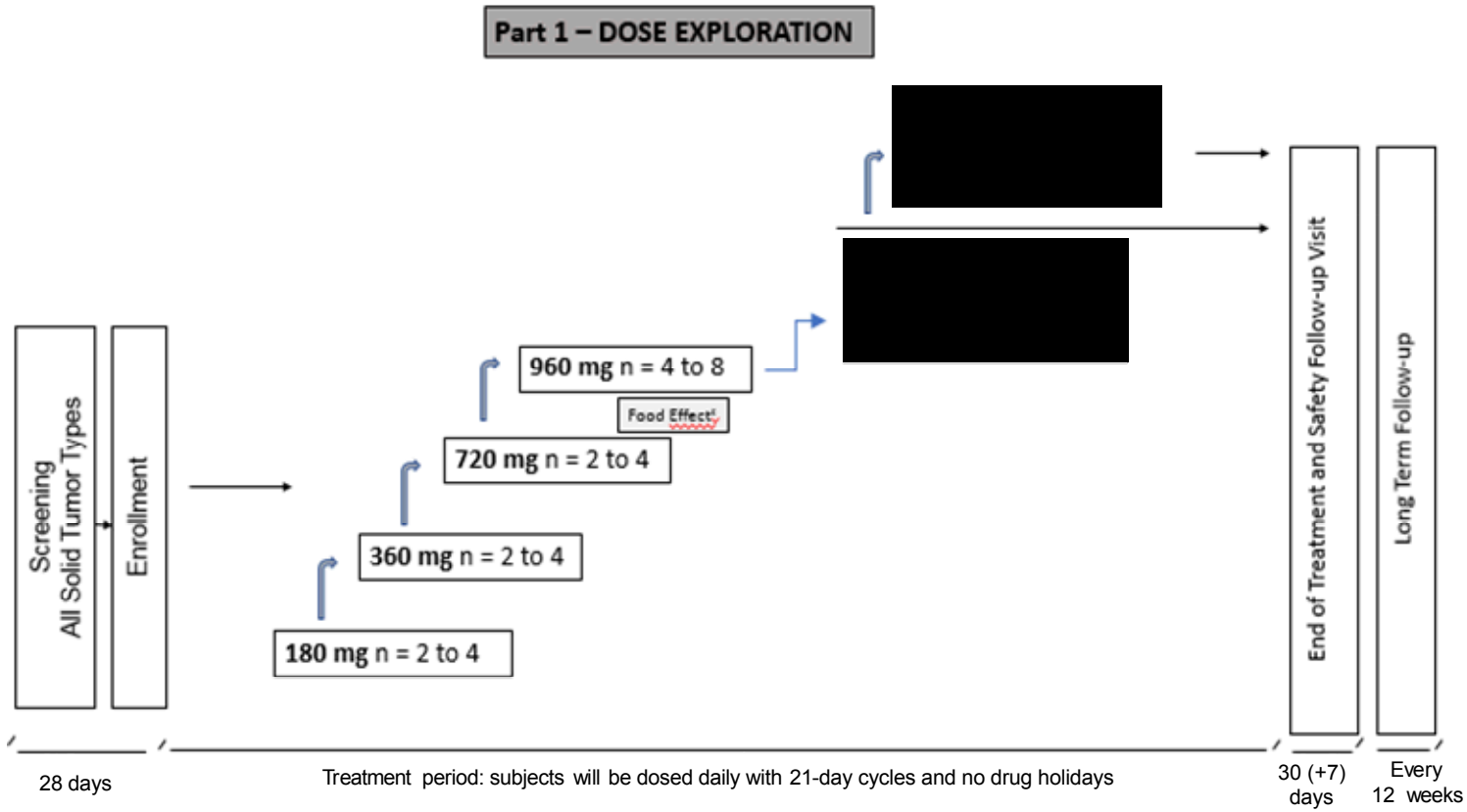
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen Inc.

Data element standards version: 6.0

Schema. Study Design and Treatment

Figure 1. Phase 1 Part 1 – Dose Exploration Schema



Footnotes defined on next page

DLRT = Dose Level Review Team; DLT = dose limiting toxicity; EOT = end of treatment; MTD = maximum tolerated dose; NSCLC = non-small cell lung carcinoma; PK = pharmacokinetic(s); TBD = to be determined.

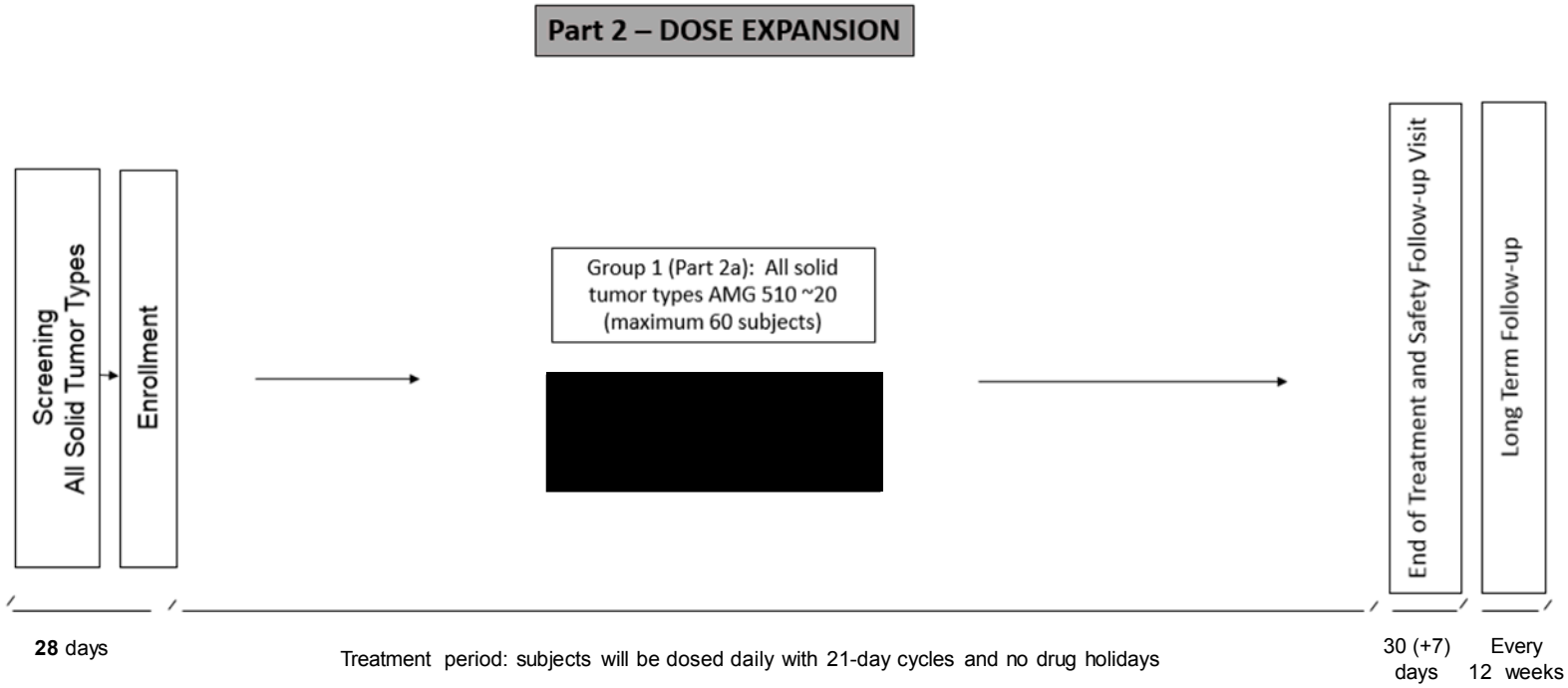
Note: DLT window is 21 days. Additional subjects may be enrolled in 1 or more dose levels that have been shown to be safet and tolerable (backfill enrollment)

[a] [redacted]

[c] **Optional f**ood **effect assessment** will be conducted in at least 6 subjects **from monotherapy dose exploration or expansion cohorts (preferably from 960 mg cohort)** in cycle 2 or later.

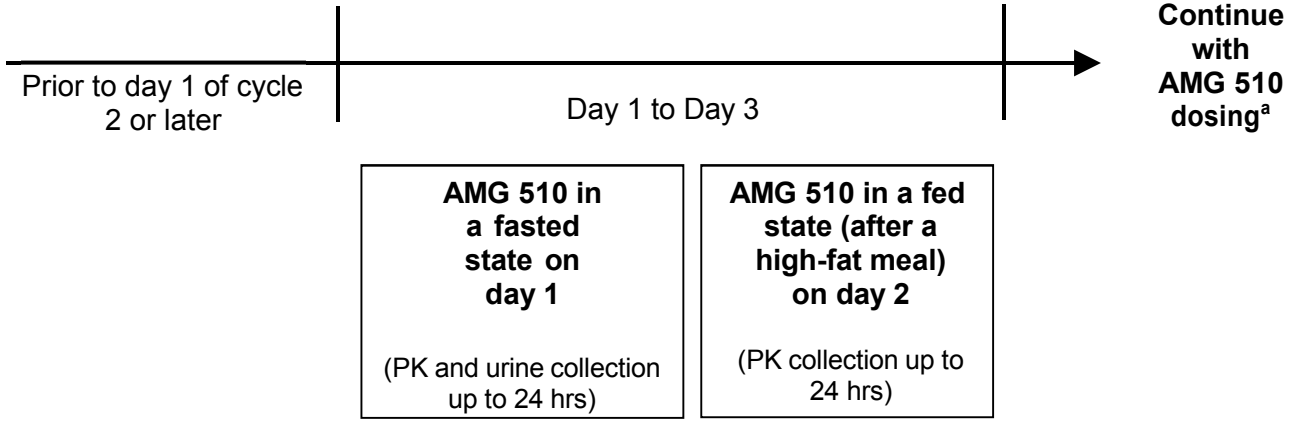
[d] Japanese subjects will be enrolled in the dose exploration portion of the study and treated at the MTD or RP2D.

Figure 2. Phase 1 Part 2 – Dose Expansion Schema



EOT = end of treatment; NSCLC = non-small cell lung carcinoma.

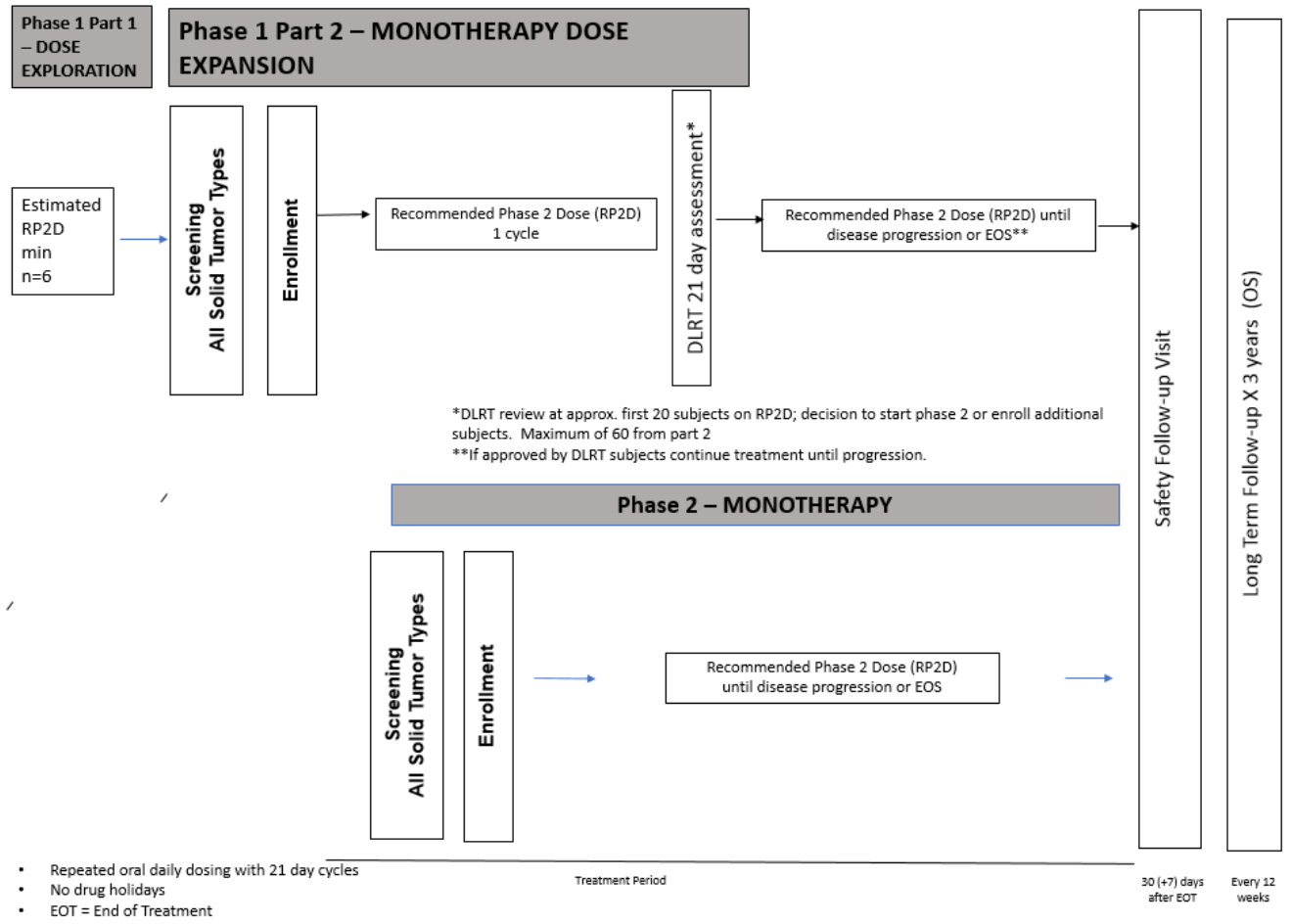
Figure 3. Food Effect Assessment Schema (Phase 1 Part 1a or Part 2a)



PK = pharmacokinetic.

[a] Administration of AMG 510 may continue until **subject has confirmed** disease progression, **or discontinues from the treatment for reasons listed in Section 8.3.1**.

Figure 4. Transition From Phase 1 to Phase 2 Study Schema



DLRT = Dose Level Review Team; EOS= end of study; EOT = end of treatment; MTD = maximum tolerated dose; OS = overall survival; RP2D = Recommended Phase 2 Dose.

DLRT will be responsible for reviewing data in the dose expansion phase to confirm the RP2D and determine the benefit/risk of proceeding to the phase 2 part of the study according to the futility and efficacy threshold guidance described in Section 10.4.1.

Study Glossary

Abbreviation or Term	Definition/Explanation
ANC	absolute neutrophil count
AUC	area under the plasma concentration-time curve
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BID	twice daily
BLRM	Bayesian Logistics Regression Model
C_{max}	maximum plasma concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte associated protein 4
CYP3A	cytochrome P450 3A
DCR	disease control rate
DDI	drug-drug interaction
DL	dose level
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DLT	dose limiting toxicity
DILI	drug induced liver injury
DOR	Duration of response
DRT	Data Review Team
ECG	electrocardiogram
EQ-5D-5L	EuroQol-5 Dimension
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 study
End of Study	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 (eg, long-term follow-up), as applicable
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

Abbreviation or Term	Definition/Explanation
End of Treatment	defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30
ERK	extracellular signal-regulated kinase
Exposure-Response Analysis	mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic [PK] exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic effects, efficacy and safety endpoints
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FOLFIRI	folinic acid, 5-fluorouracil, and irinotecan hydrochloride
FOLFOX	folinic acid, 5-fluorouracil and oxaliplatin
GAP	GTPase-activating protein
GCP	Good Clinical Practice
GDP	guanosine diphosphate
GTP	guanosine triphosphate
HBs	hepatitis B surface antibody
HepBsAg	Hepatitis B surface antigen
HepCAb	Hepatitis C antibody
HLA	human leukocyte antigen
HNSTD	highest non-severely toxic dose
HRQOL	Health-related Quality of Life
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin
IgV	Ig Variable-type
IPIM	Investigational Product Instruction Manual
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)

Abbreviation or Term	Definition/Explanation
$KRAS^{G12C}$	KRAS protein with a G12C mutation at the protein level
KRAS p.G12C	*KRAS* DNA with a mutation resulting in a G12C mutation at the protein level
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NOEL	no observed effect level
NRAS	neuroblastoma RAS viral oncogene homolog
NSCLC	non-small cell lung carcinoma
OR	overall response
ORR	objective response rate
OS	overall survival
PET	positron emission tomography
PD	Progressive disease
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
P-gp	P-glycoprotein
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PO	oral(ly)
PFS	progression-free survival
PR	partial response
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), whether the study concluded as planned in the protocol or was terminated early
PRO	patient-reported outcomes
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
Q3W	every 3 weeks
QD	once daily
QLQ-LC13	Quality-of-Life Questionnaire Lung Cancer Module
QLQ-PAN26	Quality-of-Life Questionnaire Pancreatic Cancer Module
QOL	Quality of Life
QTc	corrected QT (interval)

Abbreviation or Term	Definition/Explanation
RAF	RAF proto oncogene serine/threonine-protein kinase
RAS	rat sarcoma viral oncogene homolog
RECIST	**response evaluation criteria in solid tumors**
RNAi	RNA interference
RP2D	recommended phase 2 dose
SD	stable disease
STD_{10}	severely toxic dose in 10% of animals
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.
Study Day 1	defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
$t_{1/2,z}$	terminal half-life
TBL	total bilirubin
t_{max}	time to achieve C_{max}
TGI	tumor growth inhibition
TPI	toxicity probability interval
TPS	Tumor Proportion Score
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor

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1. OBJECTIVES

1.1 Phase 1 (Monotherapy – Parts 1a, 1b, and 2a)

1.1.1 Primary

- To evaluate the safety and tolerability of AMG 510 in adult subjects with *KRAS p.G12C* mutant advanced solid tumors
- To estimate the maximum tolerated dose (MTD) and/or a recommended phase 2 dose (RP2D) in adult subjects with *KRAS p.G12C* mutant advanced solid tumors

1.1.2 Secondary

- To characterize the pharmacokinetics (PK) of AMG 510 following administration as an oral tablet formulation
- To evaluate tumor response assessed by response evaluation criteria in advanced solid tumors (**RECIST**) 1.1 of AMG 510 as monotherapy in advanced solid tumors with *KRAS p.G12C* mutation
- To evaluate the effect of food on the oral PK of AMG 510
- To evaluate the relationship between changes in corrected QT interval (QTc) and AMG 510 exposure

1.1.3 Exploratory

- To explore pharmacodynamic relationships for safety and/or efficacy endpoints
- To characterize AMG 510 excretion in urine
- To identify metabolites of AMG 510 in plasma and urine
- To investigate potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor tissue samples.

[redacted]

1.3 Phase 2 (AMG 510 Monotherapy)

1.3.1 Primary Objective

- To evaluate tumor objective response rate (ORR) assessed by **RECIST** 1.1 criteria of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutated advanced tumors (NSCLC, colorectal cancer [CRC], and other tumor types).

1.3.2 Secondary Objectives

- To evaluate other measures of AMG 510 efficacy as monotherapy in subject with *KRAS p.G12C* muta**nt** advanced tumors by **RECIST** 1.1 (NSCLC, CRC, and other tumor types).
  - Duration of response (DOR)
  - Disease control rate (DCR)
  - **Time to response (TTR)**
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - PFS rate at 6 months and 12 months
  - OS rate at 12 months
- To evaluate the safety and tolerability of AMG 510 in adult subjects with *KRAS p.G12C* mutant advanced solid tumors (NSCLC, CRC, and other tumor types).
- To evaluate the PK of AMG 510 following administration as an oral tablet formulation

1.3.3 Exploratory Objectives

- To explore PK/pharmacodynamic relationships for safety and/or efficacy endpoints
- To explore biomarkers of response and resistance in tumor and blood specimens prior to exposure to AMG 510 and at the time of progression
- To explore the subject experience with AMG 510 treatment using patient-reported outcome instruments with respect to the following core concepts:
  - Impact of treatment on disease-related symptoms and Health-related Quality of Life (HRQOL)
  - Treatment-related symptoms and impact on the subject
  - Physical function

2. BACKGROUND AND RATIONALE

2.1 Oncogenic RAS Driven Tumorigenesis - Background

The rat sarcoma (*RAS*) proto-oncogene has been identified as an oncogenic driver of tumorigenesis in both NSCLC and CRC (Der et al, 1982; Smith et al, 2010; Johnson et al, 2001). The RAS family consists of 3 closely related genes that express GTPases responsible for regulating cellular proliferation and survival (Barbacid et al, 1987; Simanshu et al, 2017). The RAS proteins, Kirsten rat sarcoma viral oncogene homolog (KRAS), Harvey rat sarcoma viral oncogene homolog (HRAS),

and neuroblastoma RAS viral oncogene homolog (NRAS) (Hall et al, 1983; Taparowsky et al, 1983; Chang et al, 1982; Kirsten and Mayer, 1967; Harvey, 1964), can be mutationally activated at codons 12, 13, or 61, leading to human cancers. Different tumor types are associated with mutations in certain isoforms of *RAS*, with *KRAS* being the most frequently mutated isoform in most cancers (Prior et al, 2012). While the role of *KRAS* mutations in human cancers has been known for decades, no anti-cancer therapies specifically targeting *KRAS* mutations have been successfully developed, largely because the protein is intractable for inhibition by small molecules (McCormick, 2016).

2.2 KRAS p.G12C Mutation and AMG 510

Of the *KRAS* mutations, it is estimated that approximately 80% occur at codon 12 (Prior et al, 2012). The *KRAS p.G12C* mutation is estimated to occur in approximately 13% of lung adenocarcinoma (including NSCLC), 3% of CRC, and 1% to 2% of numerous other solid tumors (including pancreatic, endometrial, bladder, ovarian, and small cell lung tumors) (Biernacka et al, 2016; Neumann et al, 2009; The AACR Project GENIE Consortium, 2017). This specific mutation has been identified as a putative oncogenic driver in several types of solid tumors including NSCLC (Fernández-Medarde and Santos, 2011) and CRC (Jones et al, 2017) and other solid tumors such as pancreatic, endometrial, bladder, ovarian, and small cell lung tumors (Zhou et al, 2016; The AACR Project GENIE Consortium, 2017).

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

AMG 510 is a small molecule that specifically and irreversibly inhibits the $KRAS^{G12C}$ 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 which covalently modifies the cysteine residue and locks $KRAS^{G12C}$ in an inactive, guanosine diphosphate (GDP)-bound conformation. This blocks the interaction of KRAS with effectors such as RAF proto oncogene serine/threonine-protein kinase (RAF), thereby preventing downstream signaling, including the phosphorylation of extracellular signal-regulated kinase (ERK) (Cully and Downward, 2008; Ostrem et al, 2013; Simanshu et al, 2017). Inactivation of KRAS by RNA interference

(RNAi) or small-molecule inhibition has previously demonstrated an inhibition of cell growth and induction of apoptosis in tumor cell lines and xenografts harboring *KRAS* mutations (including the *KRAS p.G12C* mutation) (Janes et al, 2018; McDonald et al, 2017; Xie et al, 2017; Ostrem and Shokat, 2016; Patricelli et al, 2016). Studies with AMG 510 have confirmed these in vitro findings and have likewise demonstrated inhibition of growth and regression of cells and tumors harboring *KRAS p.G12C* mutations (Section 5.1). These data suggest that inhibition of *KRAS p.G12C* may have therapeutic benefit for subjects with KRAS p.G12C-driven cancers. Accordingly, the first-in-human (FIH) **and Phase 2** Study 20170543, will evaluate the safety, tolerability, PK, and efficacy of AMG 510 in subjects with *KRAS p.G12C* mutant advanced NSCLC, CRC, and other solid tumors.

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

Worldwide, lung cancer (small cell and non-small cell) and CRC are the first and third most common types of cancer occurring in both men and women (WHO statistics, 2015). It is estimated that in 2018 there **were** approximately 234 030 new cases of lung cancer and 140 250 new cases of CRC in the United States (US) alone (American Cancer Society, 2018). The 5-year survival rate for advanced NSCLC cancer is between 1% and 10% depending on the stage. Similarly, the 5-year survival rate for advanced CRC is approximately 11% (American Cancer Society, 2018). Therefore, while the incidence of the G12C KRAS mutation in these tumor types is relatively low (approximately 13% and 3%, respectively) the overall incidence of NSCLC and CRC and the poor prognosis of subjects with advanced/metastatic disease makes this mutation an important molecular target.

There is currently no anticancer therapy specifically targeting tumors that harbor the *KRAS p.G12C* mutation. Subjects with metastatic or unresectable NSCLC, CRC and other solid tumors (including pancreatic, endometrial, bladder, ovarian, appendiceal, ampullary, and small intestine) with the *KRAS p.G12C* mutation are generally being 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, 2018a) followed by second line therapy with a taxane with or without a VEGF inhibitor.

Although somatic mutations in *EGFR, BRAF,* and *HER*2, and rearrangements in *ALK, ROS,* and *RET* have been validated as powerful predictive biomarkers, and have

expanded treatment options for these molecularly defined subsets of subjects, since the KRAS mutation rarely occurs concomitantly with these other molecular abnormalities, subjects with KRAS mutations are not usually candidates for these therapies (Scheffler et al, 2018; Gainor et al, 2013). Efforts to target KRAS mutant NSCLC by inhibiting downstream signaling mechanisms such as MEK1/2 or CDK4/6 inhibitors have been unsuccessful to date (Roman et al, 2018). More recently, NSCLC subjects with the *KRAS p.G12C* mutation are, like subjects without other molecularly defined targets, receiving anti-programmed cell death-1 (PD-1) inhibitors with or without chemotherapy in first and/or second line therapy.

A similar situation exists for CRC subjects with the *KRAS p.G12C* mutation albeit due to lack of other effective therapies, chemotherapy with or without bevacizumab remains the standard of care in first and second line. While EGFR inhibitors are an option for some subjects, they are not effective in subjects with KRAS mutations (Douillard et al, 2013; Amado et al, 2008; Karapetis et al, 2008). Anti-PD1 inhibitors appear to be effective in CRC subjects who are microsatellite instability-high (MSI-H); however, this appears to constitute only approximately 5% to 15% of all CRC subjects (Fabrizio et al, 2018; Vanderwalde et al, 2018; Vilar and Gruber, 2010).

Preliminary literature review performed by Amgen on *KRAS p.G12C* mutant subjects (from 15 publications with NSCLC and 4 publications with CRC G12C specific data over the past 10 years) suggests that in general, in NSCLC subjects, the *KRAS p.G12C* mutation appeared to be associated with poorer progression-free and disease-free survival; in CRC subjects the *KRAS p.G12C* mutation appeared to be associated with less favorable survival outcomes. However, the magnitude of these differences was modest and there were a few studies that reported no difference or slightly better outcomes of subjects with *KRAS p.G12C* mutations. Amgen is performing a systematic literature review for treatment outcomes (ie, OS, PFS, ORR, DOR, etc) in *KRAS* and more specifically *KRAS p.G12C* mutant cancer subjects.

Amgen has also initiated 2 real-world data studies utilizing AACR project GENIE and Syapse genomic and linked EMR data. AACR GENIE (~850 *KRAS p.G12C* subjects) and Syapse (~1,000 *KRAS p.G12C* subjects) will provide real world evidence on subject characteristics, treatments, and outcomes (OS, PFS, etc). These data will be used to provide context for the results **that will be** observed in the phase 1/2 trial of AMG 510 study. Results of these studies and the systematic literature review are anticipated to be available prior to primary analysis of this phase 1/2 trial of AMG 510.

Pending the results of these investigations and based on the preliminary literature review described above, Amgen will assume that subjects with the *KRAS p.G12C* mutation respond similarly to chemotherapy, immunotherapy, and anti-angiogenic agents as subjects who do not harbor a *KRAS p.G12C* mutation.

For advanced/metastatic NSCLC subjects, multiple large phase 3 trials have demonstrated ORR in ≥ second line (following first line platinum-containing chemotherapy doublets, typically cisplatin/pemetrexed) of 5.5 to 13 % with chemotherapy (typically a taxane) and 9.7 to 22.5 % with chemotherapy plus a VEGFR inhibitor (Gridell et al, 2018; Rittmeyer et al, 2017; Herbst et al, 2016; Borghaei et al, 2015; Herbst et al, 2007). These trials have also demonstrated PFS of 2.8 to 4.2 months and 4.8 to 5.4 months and OS of 6 to 11.4 months and 9.9 to 12.6 months for chemotherapy and chemotherapy plus a VEGFR inhibitor, respectively. Recent studies of ≥ second line NSCLC subjects receiving anti-PD1 therapy (post-chemo doublet therapy in first line) have yielded more substantial ORR and OS (Vokes et al, 2018; Herbst et al, 2016; Borghaei et al, 2015); however, due to recent approvals of anti-PD1 therapy for first line NSCLC the sequence of immunotherapy in NSCLC is in flux and the standard of care (and outcomes) for subjects who progress or recur after first line anti-PD1 therapy remains unclear.

In the case of advanced or metastatic RAS mutant CRC, standard of care therapy for second line subjects is generally folinic acid, 5-fluorouracil and oxaliplatin (FOLFOX) or folinic acid, 5-fluorouracil, and irinotecan hydrochloride (FOLFIRI) with or without the addition of a VEGF inhibitor with approximately 6% ORR, PFS of 5.3 to 7.7 months and OS of 11.2 to 14.1 months (Masi et al, 2015; Iwamoto et al, 2015; Bennouna et al, 2013; Giantonio et al, 2007; Tournigand et al, 2004). For subjects who have progressed or recurred after both FOLFOX and FOLFIRI with addition of a VEGF inhibitor (ie, ≥ 3 line), chemo doublets, Regorafenib, or Trifluridine plus Tipiracil are options however ORR with these therapies is 1 to 4%, PFS 2 to 3 months and OS 6 to 9 months (Li et al, 2015; Mayer et al, 2015; Grothey et al, 2013). Treatment options, response and survival for advanced/metastatic appendiceal and small intestinal cancers appear to be similar to those of advanced/metastatic CRC. EGFR inhibitors are not recommended for subjects with KRAS mutations and although anti-PD1 inhibitors have been shown to be effective in MSI-H CRC this constitutes only approximately 5% to 15% of all CRC subjects (Fabrizio et al, 2018; Vanderwalde et al, 2018; Vilar and Gruber, 2010). Advanced/metastatic pancreatic cancers are generally treated in first line with folinic

acid, 5-fluorouracil, irinotecan hydrochloride, and oxaliplatin (FOLFIRINOX) or gemcitabine plus nab-paclitaxel. Depending on which of these therapies is used in first line, the alternate is the likely second line therapy of choice. In subjects treated with a gemcitabine-based therapy in first line, recent studies with 5FU based therapies have resulted in ORR of 8.5 to 13.2%, PFS of approximately 2.9 to 3.1 months and OS of 4.2 to 9.9 months.

[redacted]

2.3 Amgen Investigational Product Background

AMG 510 is a small molecule that specifically and irreversibly inhibits the $KRAS^{G12C}$ 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 which covalently modifies the cysteine residue and locks $KRAS^{G12C}$ in the inactive GDP-bound conformation. This blocks the interaction of KRAS with effectors like RAF, thus preventing downstream signaling, including the phosphorylation of ERK (Ostrem et al, 2013; Simanshu et al, 2017). Inactivation of KRAS through a small molecule inhibitor has previously demonstrated an inhibition of cell growth and induction of apoptosis in tumor cell lines and xenografts with the *KRAS p.G12C* mutation (Ostrem and Shokat, 2016; Patricelli et al, 2016; Janes et al, 2018). Likewise, studies of AMG 510 have demonstrated inhibition of growth and regression of cells and

tumors harboring *KRAS p.G12C* (Section 2.2.1). These data suggest that inhibition of $KRAS^{G12C}$ may have therapeutic benefit for subjects with *KRAS p.G12C*-driven cancers. Accordingly, the FIH **and Phase 2** Study 20170543, will evaluate the safety and efficacy of AMG 510 in subjects with *KRAS p.G12C* mutant advanced NSCLC, CRC, and other solid tumors

2.3.1 AMG 510 Preclinical Experience

In vitro AMG 510 inhibited nucleotide exchange of recombinant mutant $KRAS^{G12C/C118A}$ (half maximal inhibitory concentration, IC_{50} = 0.09 μM), but had minimal effect on $KRAS^{C118A}$, which is wildtype at G12. In cells, AMG 510 covalently modified $KRAS^{G12C}$ and inhibited KRAS signaling as measured by phosphorylation of ERK1/2 in all *KRAS p.G12C*-mutant cell lines tested (IC_{50} values from 0.01 to 0.12 μM), but did not inhibit phospho-ERK1/2 in cell lines with various other *KRAS* mutations. AMG 510 also impaired viability in all but one *p.G12C*-mutant cell lines (IC_{50} values from 0.004 to 0.032 μM), but did not affect the viability of cell lines that did not harbor the *KRAS p.G12C* mutation. The cellular k_{inact} and K_i values for AMG 510 were also experimentally determined in MIA PaCa-2 cells to be 0.00133 sec^{-1} and 6.97×10^{-7} M, respectively, with k_{inact}/K_i ratio of 1.9×10^{3} M^{-1} sec^{-1}.

In vivo AMG 510 covalently modified $KRAS^{G12C}$ and significantly inhibited phosphor-ERK1/2 in human *KRAS p.G12C* MIA PaCa-2 T2 pancreatic and *KRAS p.G12C* NCI-H358 NSCLC tumor xenografts in mice in a dose-dependent manner at doses as low as 1 mg/kg in the MIA PaCa-2 T2 model. After a single, 10 mg/kg dose in mice bearing MIA PaCa-2 T2 tumors, exposure of AMG 510 peaked at 0.5 hours, followed closely by maximal inhibition of phospho-ERK1/2 by 1 hour to 2 hours.

Covalent modification of $KRAS^{G12C}$ by AMG 510 tracked with inhibition and maximal modification occurred after 2 hours. Significant inhibition and modification of $KRAS^{G12C}$ persisted for 48 hours after a single, 10 mg/kg dose. In tumor xenograft studies AMG 510 significantly inhibited the growth of MIA PaCa-2 T2 and NCI-H358 tumors at doses as low as 3 mg/kg and achieved 62% and 49% regression, respectively, at 100 mg/kg. Notably AMG 510 had no effect on SW480-1AC (*KRAS p.G12V*) tumor xenografts at 100 mg/kg and did not impact body weight in any study.

2.3.2 Pharmacokinetics

AMG 510 was characterized in vitro and in vivo preclinical studies. AMG 510 exhibited moderate to high clearance (CL), moderate volume of distribution (V_{ss}), and terminal

elimination half-life ($t_{1/2,z}$) of 0.34 to 0.71 hours in animal species. The oral bioavailability of the suspension formulation was variable, ranging from 3.3 to 47% across the species tested. AMG 510 has moderate binding to plasma proteins in all species including humans. AMG 510 did not preferentially distribute into red blood cells in mouse, rat, dog, and human whereas it was preferentially distributed into red blood cells in monkey.

These data were used to predict the human AMG 510 PK parameters AMG 510 was predominantly eliminated in preclinical species in vivo through CYP3A-catalyzed formation of the metabolite, M24. M24 has > 1000-fold less pharmacological activity than its parent, AMG 510. AMG 510 was also a substrate of P-glycoprotein in vitro.

AMG 510 has a potential to cause CYP3A-mediated drug-drug interaction (DDI) due to reversible and irreversible time-dependent inhibition of CYP3A and induction of CYP3A4 in vitro. M24 also has a potential to cause CYP3A-mediated drug-drug interactions due to reversible and irreversible time-dependent inhibition of CYP3A and induction of CYP3A4 in vitro. In vitro, AMG 510 was also shown to be an inhibitor of CYP2C8 and CYP2D6, but not an inhibitor of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP2E1.

M24 was an inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. In vitro, AMG 510 was shown to be an inducer of CYP2B6, CYP2C8, CYP2C9, and CYP2C19, while M24 was an inducer of CYP2B6, CYP2C8, CYP2C9 and CYP2C19.

In vitro, AMG 510 is a P-gp substrate, thus active transport by P-gp may affect AMG 510 absorption and elimination. AMG 510 is not a BCRP substrate. Additionally, AMG 510 and its metabolite M24 was identified as an inhibitor of human MATE1. AMG 510 was also an inhibitor of human OAT3, OATP1B1, MATE2-K and P-gp. Incomplete inhibition was observed up to the highest test concentration for human OAT1, OCT1, OATP1B3 and BCRP, suggesting weak inhibition. M24 was an inhibitor of human OAT1, OAT3, OATP1B1, OATP1B3, and P-gp. Incomplete inhibition was observed up to the highest test concentration for human MATE2-K and BCRP, suggesting weak inhibition.

Based on current in vitro data, AMG 510 has a potential to interact with CYP3A4 and MATE1. The DDI potential for other enzymes and transporters is expected to be low.

2.3.3 Toxicology

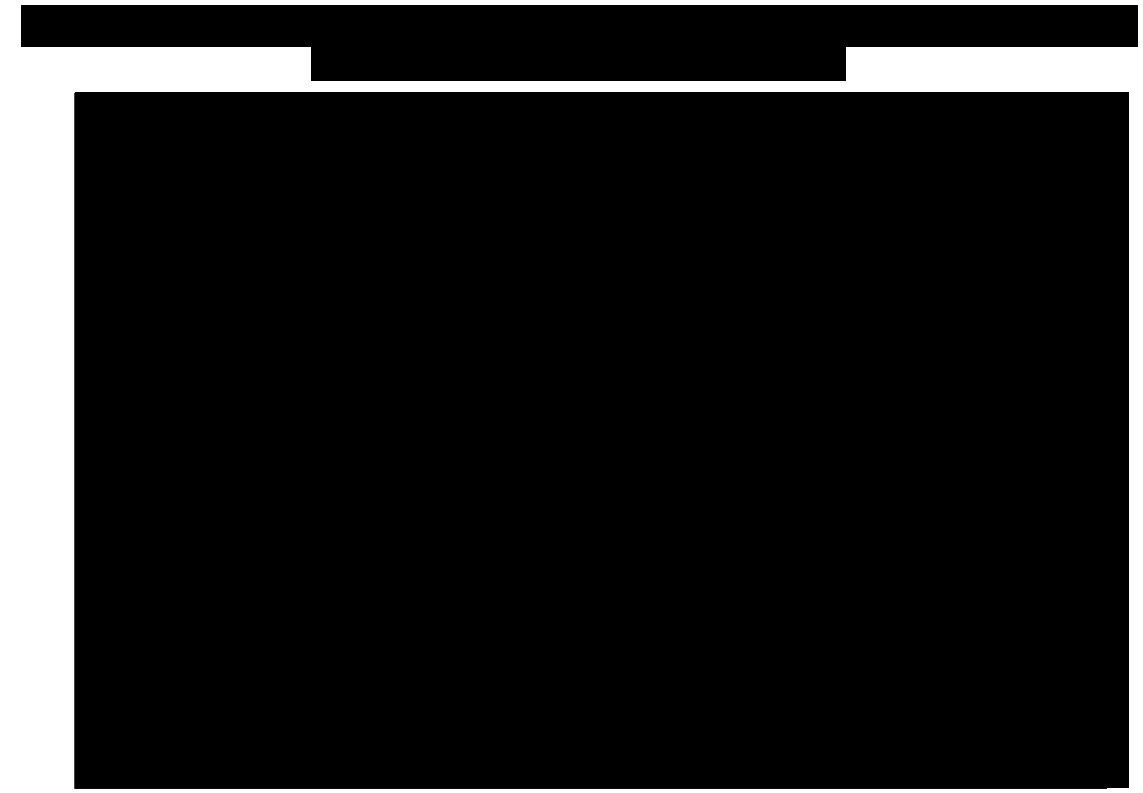
Animal toxicology studies have been completed in both the rat and dog and support development of AMG 510 for treatment of *KRAS p.G12C* mutated tumors. AMG 510 was well tolerated in the GLP 28-day rat toxicology study at 0, 10, 30, and 200 mg/kg and in the GLP 28-day dog toxicology study at 0, 10, 30, and 300 mg/kg. Key

AMG 510-related changes in the rat were minimal to mild and included kidney tubular epithelial degeneration/necrosis; increased spleen weight, increased leukocytes; and a decrease in red blood cell (RBC) mass (hemoglobin, RBC count, and hematocrit) that was associated with changes in reticulocytes and RBC indices. In the rat, AMG 510-related degeneration/necrosis of renal tubule epithelium primarily affected tubules within the outer segment of the outer medulla and was characterized by sloughing of degenerative/necrotic epithelial cells, tubular dilatation, and/or accumulation of eosinophilic material within the tubule. Reversibility data is pending in the rat. The degeneration/necrosis observed in the kidney is expected to be fully reversible based on the minimal to mild severity, the absence of tubular basement membrane damage, and the normal regenerative capacity of the renal tubular epithelium. Key AMG 510-related changes in the dog consisted of a minimal to mild decrease in RBC mass associated with decreased reticulocytes. Taken together, the AMG 510-related decrease in RBC mass and reticulocytes in the rat and dog are most likely due to red blood cell/reticulocyte destruction and not decreased hematopoietic production, given the absence of light microscopic changes in the bone marrow in dog and the increased bone marrow erythroid cellularity in a few rats. The decreases in RBC mass and reticulocytes are expected to be reversible based on the normal regenerative capacity of the hematopoietic system, and the absence of overt bone marrow toxicity (eg, hypocellularity). AMG 510 nonclinical safety studies have not identified cardiovascular concerns. Clinically significant interaction with the hERG channel are not expected over the proposed clinical dose range (hERG IC_{50} 54.8 µM). AMG 510 at doses up to 300 mg/kg did not result in changes to electrocardiogram (ECG) or hemodynamic parameters in a cardiovascular safety pharmacology study in telemetered dogs or in a 28-day toxicology study. In exploratory genetic toxicology studies, AMG 510 was not mutagenic in the Ames bacterial mutagenicity assay but was positive for clastogenicity in vitro. AMG 510 was not phototoxic in vitro.

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% of animals (STD10) in rats was > 200 mg/kg and the highest non-severely toxic dose (HNSTD) in dogs was ≥ 300 mg/kg. There was minimal toxicity at exposures up to 9-fold above those expected in humans at the highest therapeutic dose. Overall, the results of the nonclinical safety studies support the initiation of AMG 510 clinical trials and the initial clinical plan.

[redacted]

[redacted]



[redacted]

2.5 Risk Assessment

There are no identified risks associated with the administration of AMG 510. Based on nonclinical toxicity studies of AMG 510, **key safety information for** AMG 510 include**s** renal toxicity, anemia, leukocytosis, and splenomegaly. Clinical signs and symptoms of **this key safety information**, along with safety laboratories, will be monitored during the study to ensure subjects' safety.

More detailed information about the risks of AMG 510 may be found in the AMG 510 Investigator's Brochure.

2.6 Rationale

2.6.1 Phase 1

2.6.1.1 Dose Selection Rationale

The proposed AMG 510 doses are 180, 360, 720, and 960 mg administered once daily (QD) orally (PO); a twice daily (BID) PO dose may be explored as discussed in Section 3.1.1.1.2. During dose exploration (part 1) and dose expansion (part 2), AMG 510 will be given QD (or BID) PO for a treatment cycle of 21 days in length that include 21 administrations of AMG 510. The planned dose level(s) for dose expansion (MTD/RP2D) will be determined based on data collected during dose exploration.

The proposed clinical starting dose of 180 mg administered QD PO is based on the current guidance for starting dose of anti-cancer small molecule drugs (ICH S9) using the methodology described by the Food and Drug Administration (FDA) for calculating the human equivalent dose (HED) on a body surface area basis (FDA, 2005). The rat severely toxic dose in 10% of animals (STD_{10}) and the dog highest non-severely toxic dose (HNSTD) were 200 mg/kg/day PO and 300 mg/kg/day PO, respectively, as noted in the 28-day repeat-dose GLP toxicology studies. The proposed starting dose was roughly the maximum recommended starting dose of 195 mg/day PO, which is based on the lower value of $1/10^{th}$ the HED for the rat STD_{10} (195 mg/day PO) and $1/6^{th}$ the HED for the dog HNSTD (1622 mg/day PO). To estimate AMG 510 exposures in humans, AMG 510 human PK parameters were predicted using allometric scaling of PK parameters for clearance and volume obtained from nonclinical studies in mice, rats, monkeys, and dogs and absorption constant and oral bioavailability following oral tablet administration of AMG 510, the same tablet formulation to be used in this clinical study. At the starting dose of 180 mg administered QD PO, the predicted exposure margins of steady-state maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) exposures relative to the rat STD_{10} are 62-fold and 20-fold, respectively. The predicted exposure margins of steady-state C_{max} and AUC exposures relative to the dog highest severely toxic dose (HNSTD) are estimated at 50-fold and 12-fold, respectively, at the starting dose administered orally once daily.

The highest planned dose is 960 mg QD PO. The exposure margins for the predicted human steady state AUC and C_{max} exposures of this dose are 12-fold and 4-fold, respectively relative to rat STD_{10} and 9-fold and 2-fold, respectively relative to dog HNSTD. Safety and tolerability data from prior dose levels will guide the dose

escalations and the planned top dose for AMG 510 in the dose exploration phase. The MTD identified from the dose exploration phase will inform the dose expansion phase.

Efficacious doses were predicted with 2 PK/tumor growth inhibition (TGI) models that describe the anti-tumor activity of AMG 510: (1) a tumor stasis model that estimates human exposures to cause tumor stasis (ie, no net tumor growth) based on PK and TGI of MIA-PaCa-2 T2 tumor xenograft mice treated with AMG 510 and (2) a tumor regression model that utilizes clinical pancreatic cancer data and PK and TGI in AMG 510-treated MIA-PaCa-2 T2 xenograft mice to predict the treatment effects of AMG 510 on tumor growth dynamics in humans. Consolidating the results from both models, the minimal efficacious dose for AMG 510 in humans was predicted to be between 30 and 240 mg QD PO.

Integrating the toxicology, pharmacology, human PK and efficacious dose predictions, the starting dose of 180 mg QD is expected to be safe as well as potentially efficacious.

[redacted]

[redacted]

2.6.2 Phase 2

Based on preclinical PK/TGI modeling and the clinical data to date (safety/tolerability and responses described below), it is highly likely that one of the currently tested or planned monotherapy doses in phase 1 part 1 will be appropriate for expanded testing in a phase 2 trial. This protocol will allow for transition to phase 2 once an RP2D has been confirmed.

2.6.2.1 Clinical Experience – in Phase 1

The phase 1 dose exploration part of this study is ongoing. As of 24 January 2019, preliminary data were available for 22 subjects with $KRAS^{G12C}$ advanced or metastatic tumors (6 NSCLC, 15 CRC, and 1 appendiceal) who had received at least 1 dose of AMG 510: 6 subjects at 180 mg QD (dose level [DL] 1, cohort 1), 12 subjects at 360 mg QD (DL 2, cohort 2) and 4 subjects at 720 mg QD (DL 3, cohort 3). The Dose Level Review Team (DLRT) convened on 31 January 2019 and after reviewing the safety data for the subjects in the 720 mg cohort and the cumulative safety data for all the subjects, 4 subjects are allowed to enroll in cohort 4 (960 mg QD). The 5 active subjects at 180 mg were allowed to dose escalate from 180 mg to 360 mg when the 360 mg dose was declared safe and tolerable by the dose level team. Mean age of the subjects was 56 years, (female, 53 years; male, 58 years) with a mean of 4 prior therapies. Eighteen (18) subjects remain on treatment with 4 discontinuations due to disease progression after 21, 42, 62, and 72 days, respectively.

No dose limiting toxicities (DLTs) have been observed at DL 1, DL 2, or DL 3. No serious adverse events were reported up to the snap shot date. Treatment-emergent adverse events that were reported as related to AMG 510 included:

- 180 mg cohort: dry mouth, cheilitis, and hot flush (Common Terminology Criteria for Adverse Events [CTCAE] grades 1, 2, and 1, respectively)
- 360 mg cohort: pyrexia (CTCAE grade 1)
- 720 mg cohort: nausea, diarrhea (CTCAE grade 1)

No significant trends in safety labs (hematology, chemistry, coagulation, and urinalysis), ECG, or vital signs were observed.

Tumor assessment (physician assessment from computed tomography [CT] or magnetic resonance imaging [MRI]) performed at 6 and 12 weeks are shown below:

Cohort	6-week scan response	12-week scan response
Subjects at 180 mg at C1D1	SD[a]	SD[a]
	SD[b]	SD[b]
	PR[a]	PR[a]
	SD[b]	**NE**
	SD[b]	SD[b]
	SD[a]	--
Subjects at 360 mg at C1D1	PD[b]	--
	SD[b]	--
	SD[b]	--
	SD[b]	SD[b]

C1D1 = cycle 1 day 1; N**E** = not **evaluable**; **PD = progressive disease;** PR = partial response; SD = stable disease.

[a] Non-small cell lung carcinoma

[b] Colorectal cancer

2.7 Clinical Hypotheses

The following hypotheses will be tested with this clinical protocol**:**

Phase 1 (Monotherapy [redacted]

- At least **1** dose level of AMG 510, in repeat oral administrations, will achieve acceptable safety and tolerability in subjects with *KRAS p.G12C* mutant advanced solid tumors in both monotherapy [redacted]
- A favorable PK profile will be achieved with AMG 510 administered orally as monotherapy [redacted]
- Responses will be observed at a monotherapy dose level that achieves acceptable safety and tolerability.

Phase 2 (AMG 510 Monotherapy):

- A clinically relevant ORR will be observed in each tumor type (NSCLC, CRC or other tumor type) at a dose level that demonstrates acceptable safety and tolerability

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 1/2 multicenter, non-randomized, open-label study of orally administered AMG 510 in subjects with *KRAS p.G12C* mutant advanced solid tumors. The study will be conducted at approximately 100 sites globally.

Phase 1 is a FIH dose exploration/expansion study to define the MTD or RP2D, safety, tolerability, PK, and pharmacodynamics of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors **(Phase 1, Part 1a, 1b, and 2a)** [redacted] The phase 1 will be conducted in 2 parts: part 1 – Dose Exploration and part 2 – Dose Expansion. Part 1 is aimed at evaluating the safety, tolerability, PK, and pharmacodynamics and determining the MTD of repeat daily (QD) (or twice daily [BID]) dosing for AMG 510 monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors using a Bayesian Logistics Regression Model (BLRM) design (Neuenschwander et al, 2008) [redacted] The dose expansion part of the study (part 2) can open once the MTD and/or a RP2D has been determined in part 1. The DLT evaluation period will be 21 days.

Phase 2 is a multicenter, non-randomized, open-label, phase 2 study to evaluate efficacy and safety/tolerability of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors (NSCLC, CRC, and other tumors).

Administration of AMG 510 may continue until **until subject has confirmed disease progression, or discontinues from the treatment for reasons listed in Section 8.3.1**.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.1.1 Phase 1

3.1.1.1 Dose Exploration – Part 1

No more than 92 subjects will be enrolled to the dose exploration cohorts.

[redacted] **After completion of evaluation of preliminary food effect (Section 3.1.1.1.4), a**pproximately 12 subjects in 2 cohorts of n = 3-6 subjects may be enrolled to evaluate initial safety, PK and pharmacodynamics of AMG 510 using BID dosing. In order to better estimate the RP2D and to better characterize the safety,

efficacy, PK, and pharmacodynamics for AMG 510 monotherapy, an additional 20 to 40 subjects may be enrolled in one or more monotherapy dose levels that have been deemed to be safe and tolerable, defined as backfill enrollment. Subjects in backfill enrollment will be allowed to proceed to higher dose levels when the higher dose levels have been deemed safe and tolerable. This backfill enrollment may be concurrent with dose escalation to identify the MTD.

For sites in Japan, a**n additional** minimum of 3 Japanese subjects will be enrolled and treated at the MTD or RP2D in order to evaluate the tolerability of monotherapy AMG 510 in Japanese subjects. The DLRT will convene and review the safety and available PK data of the 21-day DLT evaluation period. Additional Japanese subjects will be allowed to enroll in the dose expansion and phase 2 after the DLRT confirms the safety and tolerability of AMG 510 monotherapy in Japanese subjects.

Table 1. Planned Escalation Dose Levels

Cohort	AMG 510 Dose (mg)	[redacted]
1	180	[redacted]
2	360	[redacted]
3	720	[redacted]
4	960	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted] MTD = maximum tolerated dose; NA = not available; [redacted]
TBD = to be determined.
Note: Potential intermediate doses of 270 mg and 540 mg [redacted]

3.1.1.1.1 Part 1a Monotherapy Cohorts (Once Daily Dosing – QD)

Dose exploration monotherapy cohorts will estimate the MTD or R2PD and evaluate the safety, tolerability, PK, and pharmacodynamics of different doses of AMG 510 administered orally QD in subjects with *KRAS p.G12C* mutant advanced solid tumors. Enrollment into the dose exploration cohorts may be from any eligible *KRAS p.G12C* mutant solid tumor type. Dose escalation will begin with 2-4 subjects treated at the lowest planned dose level of 180 mg. Dose escalation will follow the planned schedule with 2-4 subjects treated in each cohort. If no DLT is observed, dose escalation will

continue to the next planned dose cohort as per Table 1. **In addition to the dose levels outlined in Table 1, intermediate doses of 270 mg and 540 mg may be explored.** Upon escalation to the next planned dose cohort, sentinel dosing will apply. There will be a 2 day window between the first subject dosed and subsequent subjects. Once a subject experiences a DLT, dosing for subsequent cohorts will be recommended using the dose level recommendation from the BLRM. After each cohort, the model's recommended MTD dose level for evaluation is the dose level with the highest probability of the target toxicity probability interval (TPI), but with a less than 0.25 probability of an excessive TPI. The target TPI is (0.20, 0.33], and a TPI of (0.33, 1.00] is defined as excessive. The decision to advance to the next dose level will be recommended by the DLRT using the dose level recommendation from BLRM, as appropriate, and by evaluating available safety data, laboratory, and PK information.

Intra-subject dose escalations are allowed in this study. Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle if the next dose cohort is deemed safe at that time by the DLRT and after consultation with the sponsor if:

- no DLT has been reported for this subject during or after completion of the DLT period
- the subject has not experienced any ≥ grade 2 adverse events (deemed treatment related by the investigator) during treatment

Subjects who proceed to a higher dose level will be required to have back to back clinic visits on day 1 and day 2 at the beginning of the cycle with the higher dose. The safety assessments of chemistry and urinalysis will be performed on day 1 and day 2. A repeat of PK sample collection will be performed as on cycle 1 day 1 and cycle 1 day 2, regardless of actual study cycle.

Subjects who do not proceed to a higher dose may continue to receive additional cycles at the original dose.

Dose exploration will continue until any of the following events.

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 DLT-evaluable subjects).
- The MTD is identified, BLRM recommends a dose level which already has 6 DLT-evaluable subjects.

Japanese subjects will be enrolled in the dose exploration portion of the study and treated at the MTD or RP2D.

3.1.1.1.2 Part 1b Monotherapy Cohorts (Twice Daily Dosing – BID)

A BID dosing schedule for AMG 510 may be investigated as a dose modification strategy to potentially optimize AMG 510 activity. The initiation of the BID dosing schedule will be based upon the totality of the data available from Part 1a **and food effect assessment**. Approximately 12 subjects may be enrolled in 2 cohorts of 3 to 6 subjects per cohort. Enrollment in Part 1b may be performed in parallel with enrollment in Part 2 (monotherapy dose expansion) **after availability of data from preliminary food effect cohort**. Select sites will be allowed to enroll subjects in Part 1b due to requirement for more intensive PK and additional safety assessments (Table 4).

[redacted]

3.1.1.1.4 Optional Food Effect Assessment (For Monotherapy Part 1a or Monotherapy Part 2a)

Food effect assessment will be conducted in at least 6 subjects from monotherapy dose exploration or expansion cohorts (preferably from 960 mg cohort) in cycle 2 or later who consent to participate in this optional evalution. On day 1 of the cycle in which the assessment will be conducted, subjects will receive their dose of AMG 510 with approximately 240 mL (8 ounces) of water under fasted conditions (no food or liquids, except water) for ≥ 10 hours prior to ingesting their dose of AMG 510 at the clinic. The subjects will fast overnight again (no food or liquids, except water for ≥ 10

hours) before returning to the clinic on day 2 to ingest their dose of AMG 510 after eating a standardized high-fat, high calorie meal. Subjects should eat the meal in 25 minutes or less; AMG 510 should be administered 30 minutes after the start of the meal and after at least 5 minutes of rest. Carryover of AMG 510 exposure from a prior dose is expected to be minimal based on the predicted half-life of AMG 510. For both days, no food is allowed for at least 3 hours **after** AMG 510 dosing.

Additional water can be consumed as desired, except for 1 hour prior to and 1 hour after AMG 510 dosing. Pharmacokinetic samples will be collected prior to dosing and at various time points over a 24-hour period after dosing on both days. Urine will be collected for the 24-hour period following day 1 dosing.

3.1.1.2 Dose Expansion – Part 2

Upon completing the dose exploration part of the study and depending on data obtained, dose expansion may proceed with 2 groups consisting of subjects with *KRAS p.G12C* mutant advanced solid tumors:

1. Part 2a subjects with *KRAS p.G12C* mutant advanced NSCLC, CRC, or other tumor types administered AMG 510 monotherapy once daily (total approximately n = 20, maximum n = 60)

[redacted]

Dose expansion in these 2 groups may be done concurrently.

3.1.2 Transition From Monotherapy Phase 1 (Part 2a) Dose Expansion to Phase 2

The dose expansion part of the study (phase 1 - part 2) can open once an MTD or a RP2D and dosing schedule has been estimated in the dose exploration part of the study (phase 1 – part 1). If no DLT is observed in phase 1 – part 1, the RP2D will be estimated based on composite review of PK, overall safety/tolerability and observed responses. Further confirmation of the RP2D dose will be sought in the phase 1 part 2 dose expansion.

In the dose expansion, additional patients will be enrolled at the RP2D estimated in the phase 1 part 1 dose exploration. After a minimum of 20 subjects have been enrolled to the initial estimated monotherapy RP2D (including subjects enrolled to the RP2D in either the dose exploration [approximately 6] or the dose expansion [approximately 14] parts of the study) and have completed the 21 day DLT period, and after a minimum of 10 of these subjects have at least 6 weeks of response data, the DLRT will review all

available safety, laboratory, PK, and efficacy (physician assessment) data (including all previous data from the dose expansion and backfill cohorts)**. Antitumor activity will also be monitored in terms of ORR by tumor types (NSCLC, CRC). Futility and efficacy thresholds will be calculated using Bayesian posterior probability approach based on the cumulative efficacy data and it will serve as a guidance to the DLRT. DLRT will** make a recommendation as to whether to proceed to the phase 2 monotherapy part of the study. Enrollment will not be held to conduct this assessment. The decision to proceed to the phase 2 monotherapy will be based on the totality of data from both exploration and expansion parts of the study. The DLRT may also recommend that additional subjects be enrolled at this estimated monotherapy RP2D or that a dose reduction or alternate dosing regimen be explored before proceeding to phase 2. After this first review has been conducted, if a decision is made to continue to obtain additional data at the initial estimated RP2D prior to proceeding to phase 2, the intervals for subsequent reviews will be determined by the DLRT but should occur within a maximum of 20 additional subjects enrolled and dosed for 21 days. The maximum number of subjects that may be enrolled to the initial estimated RP2D in the monotherapy dose expansion group, without confirmation of this dose for phase 2, will not exceed 60. If another dose (or schedule) needs to be explored, additional subjects on that dose (or schedule), up to a total of 60, may be enrolled. Based on emerging clinical efficacy data, the number of subjects with specific tumor types may be restricted/specified in the expansion part. **Whenever DLRT will review the data, the futility and efficacy thresholds will be calculated based on all the cumulative efficacy data to provide the guidance.**

A final estimate of the MTD and/or RP2D using BLRM will be evaluated and confirmed utilizing all DLT-evaluable subjects from the dose exploration and the dose expansion cohorts. For definition of DLT-evaluable, see Section 3.3.

3.1.3 Phase 2 – AMG 510 Monotherapy

This is a multicenter, non-randomized, open-label, phase 2 study to evaluate efficacy and safety/tolerability of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors (NSCLC, CRC, and other tumors). Approximately **200** subjects **(at least 105 for NSCLC and 60 CRC)** will be enrolled. **The timing to start enrollment into each tumor type will be communicated to the sites and may be gated based on Amgen's internal decision based on several factors (ie, efficacy and availability of the drug supply).** Tumor response will be evaluated employing

RECIST 1.1 criteria based on contrast enhanced CT/MRI imaging with assessments conducted by an independent radiological central laboratory. A combined efficacy analysis of all subjects enrolled to the confirmed monotherapy RP2D will be performed. Subgroup analysis of each tumor type will also be performed. Interim safety reviews will be conducted after 30, 50, 70, and 100 subjects have been enrolled and treated with AMG 510 in the phase 2 for at least 21 days (enrollment will not be held for completion of these safety reviews). Interim futility analysis will be conducted as described in Section 10.4.1.3.2. The primary analysis for the study will occur **after there are at least 105 evaluable** NSCLC subjects or **60 evaluable** CRC subjects **in the phase 2 ORR analysis set (Section 10.1.2.5)**, whichever occurs first. **The data cutoff will be decided to allow sufficient time to demonstrate durability of ORR.**

3.2 Number of Sites

This study will be conducted at approximately 100 sites globally. Sites that do not enroll subjects into an open cohort within 6 months of site initiation may be closed or replaced.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

It is anticipated that up to 158 subjects will be enrolled in the phase 1 part of the study. No more than 92 subjects will be enrolled in part 1 (dose exploration) cohorts and up to 66 subjects will be enrolled in part 2 (dose expansion) cohorts.

During part 1 (dose exploration), a subject that is not DLT-evaluable will be replaced with another subject to the same dose level. A subject is DLT-evaluable if either of the following occurs:

- Subject experienced a DLT or
- Subject does not experience a DLT and subject received at least 80% of the planned doses of investigational product within the first treatment cycle (ie, 21 days)

Subjects will not be replaced after end of the DLT period.

In phase 2, it is anticipated that approximately **200** subjects **(at least 105 subjects with NSCLC and 60 subjects with CRC)** will be enrolled . **Actual enrollment for each tumor type (NSCLC, CRC) will be based on DLRT recommendations and Amgen's internal decision.**

The rationale for the number of subjects is provided in Section 10.2.

3.4 Estimated Study Duration

3.4.1 Study Duration for Subjects

Subjects be on study for approximately 4 years: 28-day screening, 6 to 12 months on treatment, and 3 years of long-term follow up.

3.4.2 End of Study

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), whether the study was conducted as planned in the protocol or was terminated early. The primary completion date is the date when **the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint of Phase 2**.

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 (eg, long-term follow-up), as applicable.

4. SUBJECT ELIGIBILITY

4.1 Inclusion Criteria

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

102. Men or women ≥ 18 years old

103. Pathologically documented, locally-advanced or metastatic malignancy with *KRAS p.G12C* mutation identified through molecular testing. For phase 2, the mutation will be confirmed by central testing prior to enrollment.
    a. For NSCLC**:**
    Phase 1 subjects **must** have received platinum-based combination therapy **AND/OR** targeted therapies (ie, if molecular testing has identified mutations in EGFR, ALK, or proto-oncogene tyrosine-protein kinase ROS [ROS1] or expression of programmed death-ligand [PD-L1]), prior to receiving AMG 510**.**
    Phase 2 subjects must have progressed after receiving anti-PD1 or anti-PD-L1 immunotherapy (unless contraindicated) AND/OR platinum-based combination chemotherapy AND targeted therapy (if actionable oncogenic driver mutations were identified [ie, EGFR, ALK, and ROS1]). Subjects must have received no more than 3 prior lines of therapy.
    b. For CRC**:**
    Phase 1 subjects must have received at least 2 prior systemic regimens in the metastatic setting. For those CRC subjects with tumors that are MSI-H, at least 1 of the prior systemic regimens must be treatment with either nivolumab or pembrolizumab if they were clinically able to receive

inhibitors and 1 of these agents is approved for that indication in the region or country.
Phase 2 subjects must have progressed after receiving fluoropyrimidine AND oxaliplatin AND irinotecan. For those CRC subjects with tumors that are MSI-H, at least 1 of the prior systemic regimens must have included an anti-PD1 therapy if they were clinically able to receive inhibitors and 1 of these agents is approved for that indication in the region or country.

c. For advanced solid tumor types other than NSCLC or CRC, subjects must have received at least one prior systemic therapy or be intolerant or ineligible for available therapies known to provide clinical benefit.

104. Subjects willing to provide archived tumor tissue samples (formalin fixed, paraffin embedded [FFPE] sample collected within 5 years) or willing to undergo pretreatment tumor biopsy. Phase 1 subjects **and phase 2 subjects with tumor types other than NSCLC or CRC** with prior molecularly confirmed *KRAS p.G12C* mutation who do not have archived tissue available can be allowed to enroll without undergoing tumor biopsy upon agreement with investigator and the Medical Monitor if a tumor biopsy is not feasible.

122. Subjects who have lesions that can be feasibly biopsied will be asked to undergo a**n optional** biopsy at the time of tumor progression.

106. Measurable disease per **RECIST** 1.1 criteria (Appendix D).

107. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2 (phase 1) or ≤ 1 (phase 2)

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

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

110. QTc ≤ 470 msec (based on average of screening triplicates)

111. Adequate hematological laboratory assessments, as follows:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelet count ≥ 75 x 10^9/L
- Hemoglobin ≥ 9 g/dL **(90 g/L)**

112. Adequate renal laboratory assessments, as follows:

- Estimated glomerular filtration rate based on MDRD (Modification of Diet in Renal Disease) calculation ≥ 60 ml/min/1.73 m^2

113. Adequate hepatic laboratory assessments, as follows:

- Aspartate aminotransferase (AST) < 2.5 x upper limit of normal (ULN) (if liver metastases are present, ≤ 5 x ULN)
- Alanine aminotransferase (ALT) < 2.5 x ULN (if liver metastases are present, ≤ 5 x ULN)

- Total bilirubin < 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)

114. 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

Optional Food Effect Assessment – Specific Inclusion Criteria

115. Subject able to eat a standardized high-fat, high-caloric meal within 25 minutes

116. Subject able to fast for ≥ 10 hours

117. Subject able to handle collection of his/her urine over a 24-hour period.

Non-small Cell Lung Cancer – Specific Inclusion Criteria

118. Pathologically documented, definitively diagnosed *KRAS p.G12C* mutant NSCLC

[redacted]

Colorectal Cancer – Specific Inclusion Criteria

119. Pathologically documented, and definitively diagnosed *KRAS p.G12C* mutant CRC

Other Solid Tumor Types – Specific Inclusion Criteria

120. Pathologically documented, definitively diagnosed, *KRAS p.G12C* mutant advanced solid tumor

4.2 Exclusion Criteria

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 ≤ 2; b) on stable doses of dexamethasone, if applicable; and c) follow-up 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 ≥ 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 alimentation, uncontrolled inflammatory GI disease (eg, Crohn's disease, ulcerative colitis)

205. Active infection requiring IV antibiotics within 1 weeks 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 PCR is necessary. Detectable Hepatitis C virus RNA suggests chronic hepatitis C
207. Known positive test for HIV
208. Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to CTCAE version 5.0 grade 0 or 1, or to levels dictated in the eligibility criteria with the exception of alopecia (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
214. Major surgery within 28 days of study day 1
215. **Monotherapy with AMG 510: Men and women of childbearing potential (WOCBP) who are unwilling to practice acceptable methods of birth control during treatment and for at least 37 days (women) or 97 days (men) after receiving the last dose of AMG 510. Acceptable methods of highly effective birth control for women include sexual abstinence (refraining from heterosexual intercourse); vasectomy (women with a single male sexual partner) with testing showing there is no sperm in the semen; bilateral tubal ligation or occlusion; or intrauterine device. Acceptable methods of birth control for men include sexual abstinence (refraining from heterosexual intercourse); vasectomy with testing showing there is no sperm in the semen; bilateral tubal ligation or occlusion in the partner; or a condom (the female partner should also consider a form of birth control).**

[redacted]

[redacted]

Note: A woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.

216. Women who are lactating/breast feeding or who plan to breastfeed while on study through 37 days [redacted] after receiving the last dose of study drug.
217. Women with a positive pregnancy test.
218. Women planning to become pregnant while on study through 37 days [redacted] after receiving the last dose of study drug
219. Subject has known sensitivity to any of the products to be administered during dosing
220. Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge
221. 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
222. 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
223. Use of known cytochrome P450 (CYP) 3A4 and MATE1 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
224. Use of strong inhibitors of CYP3A4 or P-gp (including herbal supplements such as Goldenseal) within 14 days or 5 half-lives (whichever is longer) or grapefruit juice or grapefruit containing products within 7 days prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor.
225. 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.

227. 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 ≥ 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.

228. **Previous treatment with a KRAS^{G12C} inhibitor**

5. 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) (see Section 11.2). All subjects or legally acceptable representatives must personally sign and date the ICF before commencement of study-specific activities/procedures.

Subject is considered enrolled when **the investigator decides that the subject has met all eligibility criteria. The investigator decision and date of enrollment must be documented in the subject's medical records.**

The Investigator is to document the enrollment decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study receives a unique subject identification number before any study procedures are performed.

For phase 1, the subject identification number will be assigned manually and for phase 2, the subject identification number will be assigned by Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). 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.

5.1 Treatment Assignment

An Amgen representative will notify the site in writing when a cohort is open to screen new subjects.

All screening tests and procedures must be performed within 2**8** days of study day 1, unless specified otherwise in the study procedures listed in Section 7. For phase 1 only, once the site has established subject eligibility, a site representative will submit (via email) a completed subject Eligibility Worksheet to an Amgen representative. This will not be required for phase 2. The Amgen representative will acknowledge receipt of the paperwork and assign the AMG 510 dose level to confirm enrollment for that individual subject. The investigator or designee is responsible for ensuring that confirmation of enrollment from Amgen (including subject number, dose assignment and enrollment date) has been received prior to administration of study medication on day 1

The treatment assignment date is to be documented in the subject's medical record and on the enrollment CRF.

To acquire additional safety, efficacy, PK, and pharmacodynamic data to better fully inform the RP2D, an additional 20 to 40 subjects may be enrolled in one or more dose levels that have been shown to be safe and tolerable. Intra-subject dose escalations are allowed for these additional subjects. When the subject completes the DLT period the subject may proceed to a higher dose level for the following treatment cycle once the next dose cohort has been deemed safe by the DLRT and after consultation with the sponsor as described in Section 3.1. For subjects participating in food **effect assessment**, intra-subject dose escalation should not occur for at least 5 days before or during the food **effect assessment**.

6. TREATMENT PROCEDURES

AMG 510 is the Amgen investigational product used in this study.

[redacted]

6.1 Investigational Product

6.1.1 Amgen Investigational Product AMG 510

AMG 510 for phase 1 will be manufactured both by Amgen Inc. and Patheon. AMG 510 for phase 2 will be manufactured by Patheon. AMG 510 for both phases will be packaged and distributed by Amgen Inc., using Amgen clinical study drug distribution procedures. AMG 510 will be provided as 30 mg and 120 mg tablets and will be packaged in bottles of 30 tablets. A diary will be provided for subjects to record their adherence to the oral medication.

6.1.1.1 Dosage, Administration, and Schedule

AMG 510 will be administered orally once **or twice daily [BID]), depending on what phase and/or cohort of the study that the subject is enrolled. No** drug holidays **are allowed**. The effects of overdose of AMG 510 are not known. 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 2. Subjects will take AMG 510 at home on non-clinic visit days. AMG 510 must be administered in the fasted state (no food or liquids, except water, 2 hours before to 1 hour after dosing). On PK days (eg, cycle 1 day 1, cycle 1 day 8, and cycle 2 day 1 for Phase 1), subjects should eat a standard meal at least 2 hours before dosing. Subjects may eat the standard meal at home before clinic visit or in clinic.

Subject should take the AMG 510 dose at approximately the same time(s) every day. The AMG 510 dose should also not be taken more than 2 hours earlier than the **scheduled** time. A dose of AMG 510 can be replaced in the event of vomiting if the vomiting occur within 15 minutes of the dosing, all tablets administered have been accounted for (eg, 4 tablets must be collected if 4 tablets were administered) and are intact by visual inspection (not broken, partially dissolved, chewed, or crushed). **Subjects who receive AMG 510 once daily, should skip the AMG 510 dose if 6 hours have passed from the scheduled time of dosing. If a subject is enrolled to a twice daily (BID) cohort, doses should be taken approximately every 12 hours. For BID dosing, a subject should skip the AMG 510 if 2 hours have passed from the scheduled time of dosing.**

The planned dose, start date/time, stop date, quantity administered, unit, planned frequency, reason for dose change/withheld, package lot number of AMG 510 are to be recorded on each subject's CRF(s).

6.1.1.1.1 Food Effect Assessment Only

Subjects participating in the food effect assessment will receive AMG 510 in the fasted state on day 1 and fed state on day 2. Subjects in the fasted state will receive AMG 510 on an empty stomach (no food or liquids, except water) following an overnight fast of ≥ 10 hours at home prior to clinic visit for dosing. Subjects will receive AMG 510 with approximately 240 mL (8 ounces) of water. Water can be allowed as desired except for 1 hour before and 1 hour after AMG 510 administration. No food or liquid (except water) will be allowed for at least 3 hours post-dose. Subjects in fed state will be fasted overnight for at least 10 hours prior to consuming a high fat meal preferably in the clinic. Subjects should start the recommended meal approximately 0.5 hours prior to dose administration. Subjects should consume the entire meal in 25 minutes or less.

AMG 510 should be administered approximately 30 minutes after the start of the meal with approximately 240 mL (8 ounces) of water. Water can be allowed as desired except for 1 hour before and 1 hour after AMG 510 administration. No food or liquid (except water) will be allowed for at least 3 hours post dose. See specific assessments for food **effect assessment** in Table 3.

6.1.1.2 Dose-cohort Escalation and Stopping Rules (for Phase 1 Only)

After all DLT-evaluable subjects within a cohort have completed the DLT window, a Dose Level Review Meeting (DLRM) will be held to review data, monitor safety, and recommend dose change decisions. The DLRT will be composed of the investigators, Amgen Medical Monitor, Amgen Global Safety Officer, 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 decision 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 global safety officer, and all actively screening and enrolling investigators or their qualified sub-investigator designee. The team may recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), continuation or delay in dosing, repetition or expansion of a cohort, de-escalation to a lower dose, or termination of the study. This same team will be responsible for reviewing data in the dose expansion phase to confirm the RP2D and determine the benefit/risk of

proceeding to the phase 2 part of the study. The Amgen medical monitor and Global Safety Officer 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. All 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. Data to be reviewed may be unqueried.

The dosing schedule is described by a schema in the protocol synopsis.

6.1.1.2.1 DLT 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 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

DLT-evaluable is defined as completion of 80% of AMG 510 doses within the first treatment cycle (ie, 21 days). A subject who experience a DLT within the first cycle is DLT evaluable regardless of number of doses taken. If a subject is withdrawn from study for any reason other than a DLT prior to completion of the 21-day safety

observation period, a replacement subject will be assigned the same dose as the replaced subject.

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

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 with a favorable response to treatment, an option to continue at the same dose level or 1 dose level below that which the toxicity occurred can be considered. If deemed appropriate by the investigator in conjunction with the sponsor, AMG 510 treatment can resume once any non-hematological toxicity returns to the subject's baseline value or grade ≤ 1 and subject meets the following hematological requirements: ANC ≥ 1.0 x 10^9/L, platelet count ≥ 75 x 10^9/L and hemoglobin ≥ 9 g/dL. Subjects must not have received a platelet transfusion for at least 7 days prior to assessing if re-exposure to AMG 510 can occur.

If a subject is noted to have ≥ grade 3 thrombocytopenia, grade 4 neutropenia, grade 4 anemia, grade 4 leukocytosis, or ≥ grade 3 non-hematological toxicity attributable to AMG 510 at any point during study treatment, AMG 510 administration will be stopped immediately. A repeat blood collection for hematology is to be performed within 3 days. AMG 510 treatment can resume once subjects meet the following hematological requirements: ANC ≥ 1.0x 10^9/L, platelet count ≥ 75 x 10^9/L and hemoglobin ≥ 9 g/dL, leukocytosis < grade 3 and the non-hematological toxicity returns to the subject's baseline value or grade ≤ 1. Subjects requiring more than 2 weeks to recover from grade ≥ 3 toxicities will be **permanently discontinued** from the study **treatment**.

[redacted]

[redacted]

6.3 Hepatotoxicity Stopping and Rechallenge Rules (for Phase 1 and Phase 2)

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

6.4 Prior Therapies

Prior anticancer therapies must date back to the original diagnosis and will be collected through enrollment on the appropriate eCRF. 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.

6.5 Concomitant Therapy (for Phase 1 and Phase 2)

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.5.

Concomitant use of MATE1 substrates with AMG 510 may result in increase in systemic concentrations of a MATE1 substrate as AMG 510 has a potential to inhibit MATE1. Gastric acid controllers may reduce the exposure to AMG 510. Consider the risks and benefits of concomitant use. Monitor subjects receiving a MATE1 substrate or gastric acid controller with AMG 510.

In the phase 1 part of the study, Amgen will review all concomitant medications with the investigators prior to dosing with AMG 510 to ensure patient safety.

Concomitant therapies are to be collected from enrollment through the end of safety follow-up period.

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

6.6 Product Complaints (for Phase 1 and Phase 2)

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 Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

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

6.7 Excluded Treatments, Medical Device Use, and/or Procedures During Study Period (for Phase 1 and Phase 2)

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 inhibitors of cytochrome P450 (CYP) 3A4 or P-gp including herbal supplements such as Goldenseal and grapefruit juice or other grapefruit containing products
- Known strong inducers of cytochrome P450 (CYP) 3A4 including herbal supplements, such as St. John's wort
- Known cytochrome P450 (CYP) 3A4 and MATE1 sensitive substrates with a narrow therapeutic window

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, all study drugs must be discontinued, and the investigator or designee should notify the sponsor as soon as possible. A subject may be allowed to resume AMG 510 [redacted] only if both the investigator and Amgen medical monitor agree to restart study therapy.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 2. Schedule of Assessment: Phase 1 Part 1 Dose Exploration and Part 2 Dose Expansion

	Screen[a]	Treatment																																EOT[b]	SFU	LTFU
Cycle		1																						2						3,5	4,6	QC	Q2C			
Day	-28 to 1	1								2		8							9		15			1					8	1	1	1	1			
Hours (relative to dosing)		pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	pre	0	0.25	0.5	1								
GENERAL & SAFETY																																				
Informed consent	X																																			
Eligibility criteria	**X**																																			
Demographics	**X**																																			
Medical history & height	X																																			
Smoking status	X																																			
Physical exam & weight	X	X										X										X		X						X	X	X			**X**	
ECOG	X	X																						X						X	X	X		**X**	X	
Vital signs	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[c]	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**																																			
Anticancer therapy																																			**X**	**X**
Con medications		X	←==========																																	
Adverse events			←==========																																	
Serious adverse	←==========																																			

Footnotes defined on last page of the table

Table 2. Schedule of Assessment: Phase 1 Part 1 Dose Exploration and Part 2 Dose Expansion

	Screen[a]	Treatment																																		EOT[b]	SFU	LTFU
Cycle		1																						2							3,5	4,6	QC	Q2C			
Day	-28 to 1	1							2		8							9		15		1					8	1	1	1	1						
Hours (relative to dosing)		pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	pre	0	0.25	0.5	1									
Patient diaries		←==========																																				
Laboratory[d]																																						
Chemistry	X	X						X		X		X								X		X		X					X	X	X	X					
HbA1c	X																																					
Hematology	X	X						X		X		X								X		X		X					X	X	X	X					
Coagulation	X	X						X		X		X								X		X		X					X	X	X	X					
Urinalysis[e]	X	X								X		X										X		X						X	X	X					
Serum pregnancy test[f]	X																																			X	
Urine pregnancy test[f]		**X**																						**X**						**X**	**X**	**X**					
HIV	X																																					
Hepatitis serology	X																																					
DOSING																																						
AMG 510[g]		←==========																																				
[redacted]		[redacted]																																				
IMAGING ASSESSMENTS																																						
Radiological imaging (CT/MRI) and tumor assessment[i]	X																													X[i]			X[i]	X[i]		(X)[j]
MRI brain[k]	X																																					

Footnotes defined on last page of the table

Table 2. Schedule of Assessment: Phase 1 Part 1 Dose Exploration and Part 2 Dose Expansion

	Screen[a]	Treatment																																EOT[b]	SFU	LTFU
Cycle		1																						2							3,5	4,6	QC	Q2C			
Day	-28 to 1	1							2		8							9		15		1						8	1	1	1	1			
Hours (relative to dosing)		pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	pre	0	0.25	0.5	1								
PK ASSESSMENTS																																				
AMG 510 PK[l]		X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X				X		X	X	X		X			X			
BIOMARKER SAMPLES																																				
Tumor markers at site[m]		(X)																																		
Cell pellet from plasma[n]		X																																		
Plasma ctDNA[o]		X										X												X						X	X	X		X		
Serum		X										X												X						X	X	X		X		
PB Paxgene RNA		X										X												X						X	X	X		X		
Stool sample[p]		X																																X		
BIOMARKER DEVELOPMENT																																				
Tumor biopsy **(optional, as applicable)** or archived tumor tissue (FFPE) for solid tumors	X[q]																	(X)[r]																(X)[r]		

Footnotes defined on next page

BID = twice daily; CNS = central nervous system; **Con = concomitant;** CT =computed tomography; cfDNA = cell-free DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FFPE = formalin-fixed paraffin-embedded; HbA1c = hemoglobin A1c; LTFU = long-term follow-up; MRI = magnetic resonance imaging; NSCLC = non-small cell lung carcinoma; PD-L1 = programmed cell death-1; PET = positron emission tomography; **PB = peripheral blood;** PK = pharmacokinetic(s); 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); **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; PD-L1 testing in NSCLC **for Part 1c and 2c**.
[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] **Three** triplicate ECGs must be performed at screening**. For all other visits, one triplicate** ECG **must be performed. E**ach tracing **must be at least** 30 seconds apart.
[d] Assessments to be performed on day 1 of each cycle. Laboratory **a**ssessments may be performed within 24 hours before **d**ay 1 of each cycle. A window of ± 1 day is allowable for cycle 1 and cycle 2. A window of ± 2 days is allowable after cycle 2. Electrocardiograms, biomarker blood draws, safety labs, vital signs (including pulse oximetry): ± 5-minute window (for time points of 0.25 hr and 0.5 hr postdose), ± 15-minute window (all other time points).
[e] Microscopic exam required to be performed with each time point collected.
[f] **For women of childbearing potential only (defined in Criterion 215 in Section 4.2).**
[g] 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). [redacted]
[i] Radiological imaging and tumor assessments are required at screening and every 6 ± 1 weeks. 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 (Appendix D). Radiographic response (CR and PR) requires confirmation by a repeat consecutive assessment 4 weeks after the first detection of response.
[j] **For subjects who discontinued study treatment without confirmed disease progression or start of subsequent anticancer treatment, tumor assessments will continue during LTFU every 12 weeks (± 2 weeks) for up to 3 years after last subject enrolled or until confirmed disease progression, start of subsequent anticancer treatment, death, withdrawal of consent, loss to follow-up, or end of study.**
[k] All subjects with history of brain metastases 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 can 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.
[l] 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. Pharmacokinetic samples collected in cycle 3 and beyond should be performed prior to AMG 510 dosing.
[m] Tumor markers **will be performed as per standard of care and reported on the applicable eCRF**.
[n] **Cell pellet will be used for pharmacogenetics analysis in subjects who consent.**
[o] Plasma ctDNA **is to be collected as indicated in the Schedule of Assessments, and at response**.
[p] **Stool samples collected predose (-3 days) and at EOT (± 3 days).**

[q] Subjects should provide archived FFPE samples (collected within 5 years) or undergo tumor biopsy for exploratory analysis and which may include *KRAS p.G12C* mutation testing if local results are not available. PD-L1 testing will also be performed prior to enrollment for parts 1c and 2c.
[r] **After enrollment, o**ptional tumor biopsy will be performed **for subjects who consent to this assessment. It will be performed, if feasible,** on **cycle 1 day 8** at least **4** hours (± 2 hours) after dosing**, at response, and at the EOT.**

Table 3. Schedule of Assessment: Phase 1 Part 1a or Part 2a Food Effect Assessment Only

	Treatment																	
Cycle	**2 or later**																	
Day	**1**								**2**								**3**	
Hours (relative to dosing)[a]	**pre**	**0**	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**pre**	**0**	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**pre**	**0**
DOSING																		
AMG 510[b]		X								X								X
PK ASSESSMENT																		
AMG 510 PK[c]	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	
RENAL EXCRETION ASSESSMENT																		
Urine	X **(0 to 6 hours)**								X									

PK = pharmacokinetic(s).
[a] Refer to Table 2 for assessments other than for dosing and PK and renal assessments on days 1 to 3.
[b] Subjects will be administered AMG 510 on day 1 in the fasted state (no food 10 hours before dosing and 3 hours after dosing) and on day 2 in the fed state (dosing with a high fat meal). On day 3, AMG 510 can be administered with or without food per subject discretion.
[c] 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.

Table 4. Pharmacokinetic Schedule of Assessment: Phase 1 Part 1b Dose Exploration (BID dosing only)

	Screening	Treatment																														EOT
		1																					2						3,5[a]	Q2C	
Day	**-28 to 1**	**1**									**2**		**8**									**9**	**1**						**1**	**1**	
Hours (relative to dosing)[a]		**pre**	**0**	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**12**	**pre**	**0**	**pre**	**0**	**0.25**	**0.5**	**1**	**2**	**4**	**6**	**12**	**pre**	**0**	**pre**	**0**	**0.25**	**0.5**	**1**			
DOSING																																
AMG 510[b]			X							**X**		X		X								**X**		X		X				X	X	
PK ASSESSMENTS																																
AMG 510 PK[c]		X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	

BID = twice daily; EOT = end of therapy; PK = pharmacokinetic(s); Q2C = every other cycle from cycle 7 and beyond (cycles 7, 9, 11 etc).

[a] Refer to Table 2 for assessments other than for PK.

[b] AMG 510 will be administered **twice-**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). On PK days (eg, cycle 1 day 1, cycle 1 day 8, and cycle 2 day 1), subjects should eat a standard meal at least 2 hours before dosing. [redacted]

[c] 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. Pharmacokinetic samples collected in cycle 3 and beyond should be performed prior to AMG 510 dosing.

Table 5. Schedule of Assessment: Phase 2 Study Visits Through Cycle 1 Treatment

	Screening[a]	Treatment																					
Cycle		1																					
Day	**-28 to 1**	1								2		8								9		15	
Hours (relative to dosing)		pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0
GENERAL & SAFETY																							
Informed consent	X																						
Eligiblity criteria	**X**																						
Demographics	**X**																						
Medical history & height	X																						
Smoking status	X																						
Physical exam & weight	X	X										X										X	
ECOG	X	X																					
Vital signs	X	X								X		X										X	
ECG (Group A)[b, c]	X	X		X	X	X	X	X	X	X		X		X	X	X	X	X	X	X		X	
ECG (Group B)[b, c]	X	X				X						X											
Prior therapies	**X**																						
Anticancer therapy																							
Con medications	X	X	←==========→																				
Adverse events		←==========→																					
Serious adverse events	←==========→																						
Patient diaries			←==========→																				

Footnotes defined on last page of Table 6.

Table 5. Schedule of Assessment: Phase 2 Study Visits Through Cycle 1 Treatment

	Screening	Treatment																					
Cycle		1																					
Day	-28 to 1	1								2		8								9		15	
Hours (relative to dosing)		pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0
Patient-reported Outcomes																							
EORTC QLQ C30		X																					
QLQ LC13		X																					
NSCLC SAQ		**X**																					
QLQ PAN26		X																					
PRO-CTCAE		X																					
EQ-5D-5L		X																					
GP5 FACT-G		**X**																					
Laboratory[d]																							
Chemistry	X	X										X										X	
HbA1c	X																						
Hematology	X	X										X										X	
Coagulation	X	X										X										X	
Urinalysis[e]	X	X										X										X	
Serum pregnancy test[f]	X																						
Urine pregnancy test[f]		**X**																					
HIV	X																						
Hepatitis serology	X																						

Footnotes defined on last page of Table 6.

Table 5. Schedule of Assessment: Phase 2 Study Visits Through Cycle 1 Treatment

	Screening	Treatment																					
Cycle		1																					
Day	-28 to 1	1								2		8								9		15	
Hours (relative to dosing)		pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0
DOSING																							
AMG 510[g]			←==========																==========→				
IMAGING ASSESSMENTS																							
Radiological imaging, (CT/MRI) and tumor assessment[h]	X																						
MRI brain[i]	X																						
PK ASSESSMENTS																							
AMG 510 PK (Group A)[i]		X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X			
AMG 510 PK (Group B)[i]		X				X		X															
BIOMARKER SAMPLES																							
Tumor markers at site[k]		(X)																					
Plasma ctDNA[l]		X										X											
Cell pellet from plasma[m]		X																					

Footnotes defined on last page of Table 6.

Table 5. Schedule of Assessment: Phase 2 Study Visits Through Cycle 1 Treatment

	Screening	Treatment																					
Cycle		1																					
Day	-28 to 1	1								2		8								9		15	
Hours (relative to dosing)		pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0	0.25	0.5	1	2	4	6	pre	0	pre	0
BIOMARKER SAMPLES Cont.																							
Serum		X										X											
PB Paxgene RNA		X										X											
Stool sample[n]		X																					
BIOMARKER DEVELOPMENT																							
Tumor biopsy **(optional, as applicable)** or **a**rchived tumor tissue (FFPE) for solid tumors	X[o]																	**X[p]**					

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Footnotes defined on last page of Table 6.

Table 6. Schedule of Assessment: Phase 2 Study Visits Through Cycle 2 Treatment and LTFU

	Treatment													EOT	SFU	LTFU
Cycle	**2**							**3,5[a]**			**4,6**	**QC**	**Q2C**			
Day	**1**						**8**	**1**			**1**	**1**	**1**			
Hours (relative to dosing)	**pre**	**0**	**0.25**	**0.5**	**1**	**4**		**pre**	**1**	**4**						
GENERAL & SAFETY																
Physical exam & weight	X							X			X	X			**X**	
ECOG	X							X			X	X		**X**	X	
Vital signs	X															
ECG (Group A)[b, c]	X				X	X			X		X	X			X	
ECG (Group B)[b,c]															X	
Anticancer therapy															X	X
Con**comitant** medications	←==========→															
Adverse events	←==========→															
Serious adverse events	←==========→															
Patient diaries	←==========→															

Footnotes defined on last page of the table.

Table 6. Schedule of Assessment: Phase 2 Study Visits Through Cycle 2 Treatment and LTFU

	Treatment													EOT	SFU	LTFU
Cycle	2							3,5			4,6	QC	Q2C			
Day	1						8	1			1	1	1			
Hours (relative to dosing)	pre	0	0.25	0.5	1	4		pre	1	4						
Patient-reported Outcomes																
EORTC QLQ C30	X							X			X		X	**X**	X	
QLQ LC13	X							X			X		X	**X**	X	
NSCLC SAQ	**X**							**X**			**X**		**X**	**X**	**X**	
QLQ PAN26	X							X			X		X	**X**	X	
PRO-CTCAE	X							X			X		X	**X**	X	
EQ-5D-5L	X							X			X		X	**X**	X	
GP5 of the FACT-G	**X**							**X**			**X**		**X**	**X**	**X**	
Laboratory[d]																
Chemistry	X							X			X	X				
Hematology	X							X			X	X				
Coagulation	X							X			X	X				
Urinalysis[e]	X							X			X	X				
Serum pregnancy test[f]															X	
Urine pregnancy test[f]	**X**							**X**			**X**	**X**				

Footnotes defined on last page of the table.

Table 6. Schedule of Assessment: Phase 2 Study Visits Through Cycle 2 Treatment and LTFU

	Treatment													EOT	SFU	LTFU
Cycle	2							3,5			4,6	QC	Q2C			
Day	1						8	1			1	1	1			
Hours (relative to dosing)	pre	0	0.25	0.5	1	4		pre	1	4						
DOSING																
AMG 510[g]	←==========									==========→						
IMAGING ASSESSMENTS																
Radiological imaging, (CT/MRI) and tumor assessment[h]								X					X	X		**(**X**)**[q]
MRI brain[i]																
PK ASSESSMENTS																
AMG 510 PK (Group A)[i]	X				X	X		X	X	X			X			
AMG 510 PK (Group B)[i]	X				X	X		X	X	X			X			
BIOMARKER SAMPLES																
Tumor markers at site[k]	**(**X**)**															
Plasma ctDNA[l]	X							X			X	X		X		
Cell pellet from plasma[m]																

Footnotes defined on last page of the table.

Table 6. Schedule of Assessment: Phase 2 Study Visits Through Cycle 2 Treatment and LTFU

	Treatment													EOT	SFU	LTFU
Cycle	**2**								**3,5**		**4,6**	**QC**	**Q2C**			
Day	**1**								**1**		**1**	**1**	**1**			
Hours (relative to dosing)	**pre**	**0**	**0.25**	**0.5**	**1**	**4**		**pre**	**1**	**4**						
BIOMARKER SAMPLES Cont.																
Serum	X							X			X	X		X		
PB Paxgene RNA	X							X			X	X		X		
Stool sample[n]														X		
BIOMARKER DEVELOPMENT																
Tumor biopsy **(optional, as applicable)**	**(X)[p]**													X[p]		

Footnotes defined on next page

CNS = central nervous system; CT =computed tomography; cfDNA = cell-free DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; **EOT =** end of treatment; FFPE = formalin-fixed paraffin-embedded; HbA1c = hemoglobin A1c; LTFU = long-term follow-up; MRI = magnetic resonance imaging; NSCLC = non-small cell lung carcinoma; PD-L1 = programmed cell death-1; PET = positron emission tomography; **PB = peripheral blood;** PK = pharmacokinetic; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; 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); 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] **Three triplicate ECGs must be performed at screening. For all other visits, one triplicate ECG must be performed. Each tracing must be at least 30 seconds apart.**

[c] Intense ECG collection will be performed in up to approximately 30 subjects at time points described for Group A. Sparse ECG collection will be performed in the remaining subjects at time points described for Group B.

[d] Assessments to be performed on day 1 of each cycle. Laboratory **a**ssessments may be performed within 24 hours before **d**ay 1 of each cycle. A window of ± 1 day is allowable for cycle 1 and cycle 2. A window of ± 2 days is allowable after cycle 2. Electrocardiograms, biomarker blood draws, safety labs, vital signs (including pulse oximetry): ± 5 minute window (for time points of 0.25 hour and 0.5 hour postdose), ± 15-minute window (all other time points).

[e] Microscopic exam required to be performed with each time point collected.

[f] **For women of childbearing potential only (defined in Criterion 215 in Section 4.2.**

[g] 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).

[h] Radiological imaging and tumor assessments are required at screening and every 6 ± 1 weeks. After **four** 6-week response assessments, radiological imaging and tumor assessment frequency will be performed every 12 ± 1 weeks until disease progression, start of new anti-cancer treatment, death, or withdrawal of consent 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 (Appendix D). Radiographic response (CR and PR) requires confirmation by a repeat consecutive assessment 4 weeks after the first detection of response.

[i] All subjects with history of brain metastasis 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 can 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.

[j] Intense PK collection will be performed **at select sites** in up to approximately 30 subjects at time points described for Group A. Sparse PK collection will be performed in the remaining subjects at time points described for Group B. 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. Pharmacokinetic samples collected in **c**ycle 7 and beyond should be performed prior to AMG 510 dosing.

[k] **Tumor markers will be performed as per standard of care and reported on the applicable eCRF.**

[l] Plasma ctDNA **is to be collected predose as indicated in the Schedule of Assessments, and** at response.

[m] **Cell pellet will be used for pharmacogenetics analysis in subjects who consent.**

[n] Stool sample **collected predose (-3 days) and at EOT.**

[o] Subjects will provide archived FFPE samples (collected within 5 years) for *KRAS p.G12C* mutation confirmation or undergo tumor biopsy that enables *KRAS p.G12C* testing prior to starting all other screening procedures. .

[p] **After enrollment, optional tumor biopsy will be performed for subjects who consent to this assessment. It will be performed, if feasible, on cycle 1 day 8 at least 4 (± 2) hours after dosing, at response, and at the EOT.**

[q] **For subjects who discontinued study treatment without confirmed disease progression or start of subsequent anticancer treatment, tumor assessments will continue during LTFU every 12 weeks (± 2 weeks) for up to 3 years after last subject enrolled or until confirmed disease progression, start of subsequent anticancer treatment, death, withdrawal of consent, loss to follow-up, or end of study.**

7.2 General Study Procedures

Study procedures and their time points are summarized in the Schedule of Assessements (see Table 2 through Table 6). Refer to the IPIM, laboratory and site imaging manuals for detailed collection and handling procedures.

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

A signed and dated IRB/IEC approved ICF must be obtained prior to performing any study specific procedures, including discontinuing standard therapy for observing study specific washout periods.

Subjects will be seen in the clinic for study evaluations. **During all visits invasive procedures like blood draws or biopsies should be completed after ECGs, vital signs, and COAs (as applicable).**

Blood samples for biomarker and PK assessments should be drawn from a peripheral vein and not from a central venous catheter. The study specific lab manual will provide additional detail on lab sampling and handling requirements.

Study procedures should be performed and samples obtained at the time points stipulated in the Schedules of Assessments (Table 2, Table 3, Table 4, Table 5, and Table 6). Acceptable deviation windows for study procedures are listed below:

- ECGs, biomarker blood draws, safety labs, vital signs (including pulse oximetry): ± 5 minute window (for time points of 0.25 hr and 0.5 hr postdose), ± 15 minute window (all other time points)

Acceptable deviation windows for study visits are listed below:

- **v**isits during treatment**:** ± 1 day for cycle 1 and cycle 2
- **v**isits during treatment**:** ± 2 days after cycle 2
- SFU: + 7 days
- LTFU: ± 2 weeks

Furthermore, start of a treatment can be delayed for administrative/logistical reasons for up to 7 days to allow for appropriate scheduling after discussion with and final approval by sponsor.

Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the eCRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent

visits. Every effort should be taken to collect all biomarker and PK samples as described in the schedule of assessments. However, if sample processing/shipment on a weekend/holiday is not logistically feasible for a site, this needs to be documented and will not be considered a deviation from the protocol.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

Table 7. List of Analytes

<table>
<tr><th colspan="3">Local Laboratory</th><th>Central Laboratory</th></tr>
<tr><th>Chemistry</th><th>Hematology</th><th>Coagulation</th><th>PK and Biomarker</th></tr>
<tr><td rowspan="3">Sodium
Potassium
Chloride
Bicarbonate Total protein
Albumin
Calcium
Magnesium
Phosphorous
Glucose
Blood urea nitrogen
Urea[a]
Creatinine
Total creatine kinase
Total bilirubin
Direct bilirubin
Serum or Urine Pregnancy
Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
HbA1c</td><td>Hemoglobin
Hematocrit
Mean corpuscular volume
Platelets
RBC
White blood cell Differential
• Total neutrophils
• Eosinophils
• Basophils
• Lymphocytes
Monocytes</td><td>PT or INR
aPTT Fibrinogen
D-Dimer</td><td rowspan="3">PK sampling
Plasma ctDNA
Plasma cell pellet
Serum
PB Paxgene RNA
Antibody
Tumor biopsy[c]</td></tr>
<tr><td>Serology[b]</td><td>Urinalysis</td></tr>
<tr><td>HepBsAg
HepCAb
HIV

Tumor markers
-Carcinoembryonic embryonic antigen (CEA)
-Carbohydrate antigen (CA 19-9)
-Cancer antigen (CA 125)</td><td>Specific gravity, pH,
Blood protein, glucose, bilirubin, WBC, ketones, sodium, potassium
RBC, epithelial cells, bacteria
Microscopic exam:
• Cellular casts
• Granular casts
• Hemoglobin casts
• Hyaline casts
• Mixed casts</td></tr>
</table>

Footnotes defined on next page of this table

HbA1c = hemoglobin A1c; HepBsAg = hepatitis B surface antigen; HepCAb = hepatitis C antibody; INR = international normalized ratio; LDH = lactate dehydrogenase; PB = peripheraph blood; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; WBC = white blood cell count.

[a] **Urea collection is acceptable in absence of BUN.**

[b] **Hepatitis B surface antigen, hepatitis C antibody, PCR for Hepatitis C RNA (if Hepatitis C antibody is positive), and HIV assessments.**

[c] **Archived tumor tissue is acceptable. If archived tumor tissues is not available, a tumor biopsy should be performed prior to treatment.**

7.2.1 Screening

After written consent has been obtained, subjects will be screened in order to assess eligibility for study participation. All screening procedures must be performed within 2**8** 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 2**8**-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** 2**8**-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 Assessments (Table 2 ,Table 5, and Table 6).

Assessments that were performed as standard of care prior to signature of informed consent, but within 21 days 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 2**8**-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 G12C status (if applicable)**

Any other assessments do not need to be repeated if they were performed within 21 days prior to start of treatment with AMG 510.

7.2.2 Treatment

Treatment begins on Day 1 **of cycle 1** when the first **dose of** investigational product is administered to a subject.

During clinic visit days all protocol-required predose assessments have to be performed prior to administration of AMG 510.

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.

[redacted]

For phase 1, 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.

For phase 2, once a subject is confirmed as eligible and becomes enrolled, site study staff will assign and provide an eDiary (to capture compliance with AMG 510 administration). The site study staff will train the subject on how to use the eDiary (eg, turning on/off, charging, navigating screens, transmitting data, contacting the help desk for technical assistance) and complete the questions. The subject will be instructed to interact with the eDiary every day and to bring the eDiary to every study visit.

Please refer to the eDiary manual for additional details.

7.2.3 End-of-treatment Visit

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.

7.2.4 Safety Follow-up Visit

The SFU visit should occur approximately 30 (+7) days after the last dose of AMG 510 or before any new anti**cancer** treatment is started.

7.2.5 Long-term Follow-up

Following the SFU visit, there will be a**n** LTFU period **during which data will be collected on the subjects' health condition, disease status, and subsequent anticancer treatment**.

Also, for subjects who discontinued study treatment without confirmed disease progression or start of subsequent anticancer treatment, tumor assessments will continue during LTFU every 12 weeks (± 2 weeks) for up to 3 years after last subject enrolled or until confirmed disease progression, start of subsequent anticancer treatment, death, withdrawal of consent, loss to follow-up, or end of study.

Subjects who had confirmed disease progression or started subsequent anticancer treatment, will be followed via telephone every 12 weeks (± 2 weeks) for assessment of survival and documentation of anticancer treatment. Subjects will be followed for up to 3 years after last subject enrolled or until withdrawal of consent**, loss to follow-up,** or subject death, whichever occurs first.

7.2.6 End of Study Visit

End of study is defined as the date of the final study visit (eg, LTFU) when assessments and/or procedures are performed.

7.2.7 Demographics

Demographic data collection including sex, age, race, and/or ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

7.2.8 Physical Examination

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

7.2.9 Physical Measurements

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

7.2.10 Performance Status

The subject's performance status will be assessed using the ECOG PS.

7.2.11 Pharmacokinetic Blood Sampling

For PK assessment, blood samples for quantitative determination of AMG 510 will be collected at time points specified in the Schedule of Assessments (Section 7.1). Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual. For phase 2, intense PK collection will be performed at select sites in up to approximately 30 subjects at time points described for Group A. Sparse PK collection will be performed in the remaining subjects at time points described for Group B.

7.2.12 Urine Collection For Food Effect Assessment

On day 1 of the cycle in which the food effect assessment is conducted, urine will be collected **to measure active metabolites of AMG 510** for the following time periods: (1) 0 **to** 6 hours postdose, and (2) 6 **to** 24 hours postdose.

7.2.13 High-fat Meal

For the food effect assessment, the clinical site will provide standardized high-fat meal as described in the Schedule of Assessment (Table 3). A standard high-fat meal (approximately 50% of the total caloric content of the meal) and high calorie (approximately 800 to 1000 calories) meal will be used as a test meal. The test meal should derive approximately 150, 250 and 500 to 600 calories from protein, carbohydrate and fat, respectively. An example test meal would be 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces (approximately 120 mL) of hash brown potatoes, and 8 ounces (approximately 240 mL) of whole milk. Substitutions in this meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. Further details of the high fat meal will be recorded in subject medical record and eCRF.

7.2.14 Vital Signs

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

7.2.15 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 10 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. ECGs should be performed in a standardized method, in triplicate, and run consecutively, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

- ≥ 3 baseline ECGs collected **at least** ≥ 30 **seconds** apart, with each baseline ECG in triplicate run consecutively (ie, total ≥ 9 ECGs)
- Triplicate ECGs at time points after dosing

Baseline is defined as prior to dosing on cycle 1 day 1. The PI or central reader will review all ECGs. ECGs 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.

For phase 2, intense ECG collection will be performed at select sites in up to approximately 30 subjects at time points described for Group A. Sparse ECG collection will be performed in the remaining subjects at time points described for Group B.

7.3 Intensive Procedures

All subjects in phase 1 (dose exploration and dose expansion) will have intensive PK and ECG data collected. At select sites, up to a total of 30 phase 2 subjects will also be

consented to have intensive PK and ECG data collected. Please refer to Table 5 and Table 6 for timing of collection.

7.4 Clinical Laboratory Assessments

Refer to Table 7 for the list of analytes to be performed and to the Schedule of Assessments (Table 2, Table 5, and Table 6) 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 CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Table 7, must be conducted in accordance with the laboratory manual and the Schedule of Assessments (Table 2, Table 5, and Table 6).

7.5 Radiological Imaging Assessment

The extent of disease will be evaluated by contrast-enhanced MRI/CT according to **RECIST** 1.1 (Appendix D). 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. Magnetic resonance imaging (MRI) of the brain should be performed if signs or symptoms suggestive of central nervous system metastases are present.

The same imaging modality, MRI field strength and intravenous 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 ± 1 weeks for the first 4 response assessments. After **four** 6-week response assessments, radiological imaging and tumor assessment will be performed every 12 ± 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 more frequently if clinically necessitated at the discretion of the managing physician. Radiographic response (complete response, partial response) requires confirmation by a repeat, consecutive scan at least 4 weeks after the first documentation of response and may be delayed until the next scheduled scan to avoid unnecessary procedures.

All subjects with brain metastasis must have MRI of the brain performed within 28 days prior to first dose of AMG 510. Subsequently, brain scans may be performed at any time if, 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.

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

Determination of disease response for clinical management of subjects will be assessed at the clinical sites per **RECIST** 1.1. Scans will be submitted to a central imaging core laboratory for archival, response assessment including **RECIST** 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.

7.6 Patient-reported Outcomes

Patient-reported outcomes (PRO) questionnaires will be administered **via electronic tablet** to subjects enrolled into the phase 2 monotherapy part of the study.

The impact of treatment on disease-related symptoms and HRQOL will be evaluated in all subjects (regardless of tumor type) using the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30). In addition, disease specific modules will be employed: QLQ LC13 **and NSCLC SAQ** for

NSCLC, and QLQ-Pan26 for Pancreatic Cancer. Treatment-related symptoms and impact on the subject will be assessed in all subjects (regardless of tumor types) using selected questions from the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) library and a single item about symptom bother (GP5 of the FACT-G). Physical function will be assessed in all subjects regardless of tumor type using the EORTC QLQ-C30. Health-related quality of life will **also** be assessed in all subjects regardless of tumor type using the EuroQol-5 Dimension (EQ-5D-5L).

The PRO questionnaires should be completed by the subject prior to any other clinical assessments and before receiving any study medications.

The EORTC QLQ-C30 is a 2-page, self-reporting 30-item generic instrument for use in cancer subjects across tumor types. It assesses 15 domains consisting of 5 functional domains (physical, role, emotional, cognitive, social), 9 symptom domains (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a global health status or Quality of Life (QOL) scale (Aaronson et al, 1993).

The supplementary disease specific module, QLQ-LC13, is a validated questionnaire to assess the impact of treatment on lung cancer-associated symptoms (cough, hemoptysis, dyspnoea and site-specific pain) and treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication. It contains 13 questions.

The NSCLC SAQ is a 7-item instrument intended to measure overall symptom severity (eg cough, pain, dyspnea, fatigue, and appetite) of NSCLC. The NSCLC SAQ is intended to assess clinically meaningful change in overall symptoms of NSCLC and is suggested by the FDA to be used in early phase studies so that information to support thresholds for clinically meaningful, within-patient change in the NSCLC-SAQ total score can be established in the context of use.

The QLQ-PAN26 is a questionnaire **consisting of 26 items** developed to assess the **symptoms and** impact of treatment on symptoms related to pancreatic cancer . This module will be utilized to assess the small but important disease and treatment related **HR**QoL changes in pancreatic cancer. For all items on the QLQ-PAN26, except satisfaction with health care, a higher score reflected worse **HR**QoL.

PRO-CTCAE is a subject-reported outcome measure developed to evaluate symptomatic toxicity in subjects on cancer clinical trials. The questionnaire was designed to be used as a companion to the CTCAE, the standard lexicon for adverse event reporting in cancer trials. PRO-CTCAE item library version 1.0 is comprised of 124 individual questions developed to elicit 78 symptomatic AEs from subjects using between one to three attribute questions (ie, frequency, severity, and/or interference of the AE), (Basch et al, 2014). The recall period for PRO-CTCAE is the past 7 days. The PRO-CTCAE has been tested and validated in terms of construct validity, test-retest reliability, and item responsiveness (Dueck et al, 2015). In this study, the PRO-CTCAE will be administered via electronic tablet.

The specific questions which will be administered to subjects in this study will be selected from the PRO-CTCAE item library following a review of the data from the phase 1 dose exploration part of AMG 510 in *KRAS p.G12C* subjects and consideration of potential toxicities which may be relevant to future comparisons of AMG 510 to current standards of care. A customized form to collect these data will be developed using the online tool available at https://healthcaredelivery.cancer.gov/pro-ctcae/builder.html.

The GP5 of the FACT-G is a single item “I am bothered by side effects of treatment” rated on a 5-point Likert scale from “not at all” to “very much” is an item included in the Physical Well-Being subscale of the PRO assessment instrument Functional Assessment of Cancer Therapy Tool General form (FACT-G). It has been evaluated and validated as a useful summary index of side effect impact or burden to the individual subject (Pearman et al, 2018).

The EQ-5D-5L questionnaire is a 2-page, standardized instrument for use as a measure of health outcome developed by the EuroQol group (Rabin and de Charro, 2001). It is comprised of a 5-dimension health status measure and a visual analogue scale. The 5-dimension health status measure evaluates: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression based on a 5-level scale: no problems, slight problems, moderate problems, severe problems, an extreme problem. The visual analogue scale records the subject's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. The EQ-5D-5L takes about 3 minutes to complete.

7.7 Biomarker Discovery

Samples will also be collected for biomarker analysis, eg, to evaluate potential biomarkers that may correlate with treatment response.

Blood Samples

Blood samples are to be collected for biomarker development as listed in the **Section 7.1**. Plasma and/or serum may also be used for DNA, RNA, and protein expression analysis in order to correlate levels of expression with response.

Tumor Tissues

Tissue for KRAS p.G12C Testing

All subjects in both phase 1 and phase 2 are expected to have been previously identified as expressing the *KRAS p.G12C* mutation in local laboratory testing.

- For phase 1 (dose exploration and dose expansion), subjects may be enrolled based on their previous local laboratory testing. However, prior to enrollment it must be determined that there is sufficient archived tumor tissue (collected within 5 years of enrollment) for subsequent exploratory biomarker analyses. If archived tissue is not available, a tumor biopsy (core needle [NSCLC only] or excisional), if feasible, should be performed. The tumor sample should be submitted (within 2 weeks of enrollment).
- In phase 2, **subjects with NSCLC and CRC,** an archival tumor sample (collected within 5 years of enrollment) or tumor biopsy (core needle [NSCLC only] or excisional) must be submitted prior to enrollment for central laboratory testing **with the investigational Qiagen assay** for the *KRAS p.G12C* mutation as well as subsequent exploratory biomarker analyses. These subjects cannot be enrolled until results of the central laboratory testing have been reported and demonstrate that the subject has the *KRAS p.G12C* mutation.
- In both phase 1 and phase 2, tumor tissue for *KRAS p.G12C* mutation testing may be 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.

Tissue for Exploratory Biomarker Testing

For all subjects FFPE blocks or unstained slides of archived tumor tissue (collected within 5 years of enrollment) or tumor biopsy (core needle [NSCLC only] or excisional), obtained prior to treatment with AMG 510, must be submitted along with pathology reports for exploratory biomarker testing.

An optional tumor biopsy, if feasible, on cycle 1 day 8, obtained approximately 4 hours (± 2 hrs) after dosing is encouraged. Where feasible, a biopsy should be performed at **response and** the **EOT**.

All tissue should be submitted along with the corresponding pathology report.

Tissue **collection** and submission:

When a tumor biopsy is needed for enrollment: Collection of tumor tissue following local standard of care procedure for *KRAS p.G12C* testing is not expected to present any additional risk to the health, safety, and welfare of the subject.

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; either is sufficient for both the *KRAS p.G12C* testing and for exploratory biomarker studies.

Rationale for baseline, on-treatment and post progression exploratory biomarker testing

Analyses of tumor specific mutations or epigenetic changes at baseline may be performed (eg, somatic mutations) to asses potential pre-existing resistance mechanism. Tumor tissue or biopsies at baseline, on-treatment, and at progression are to be collected and pharmacodynamic changes analyzed to determine the effect of the drug on target(s) in the tumor as well as to potentially analyze molecular mechanisms associated with acquired resistance.

[redacted]

Central Testing for *KRAS p.G12C* and PD-L1

The therascreen® KRAS RGQ PCR Kit from QIAGEN is a real-time qualitative PCR assay performed on the Rotor-Gene Q MDx instrument for the detection of 7 somatic mutations in the human KRAS oncogene using DNA extracted from FFPE tissue. The mutations detected are: G12A, G12D, G12R, G12C, G12S, G12V, G13D. The therascreen® KRAS RGQ PCR Kit is an investigational in vitro diagnostic device that will be available to be used to test subjects **with NSCLC and CRC** for the *KRAS p.G12C* mutation .

Subject testing with the therascreen® KRAS RGQ Assay and Dako PharmDx 22C3 will take place at the NeoGenomics Central Testing Laboratory in Houston, Texas.

PD-L1 testing will be conducted at the central labs using the Dako PharmDx 22C3 immunohistochemistry FDA-approved kit according to the instructions for use.

Stool Samples

Stool samples will be collected to determine whether there is a relationship between microbiota diversity and response to anti-PD-1 therapy and to understand the baseline microbiota diversity in monotherapy.

7.8 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of colorectal cancer, non-small cell lung cancer, pancreatic cancer as well as other solid tumors and/or to identify subjects who may have positive or negative response to AMG 510. Pharmacogenetic samples are collected for this part of the study. Subjects who consent to this/these analysis/analyses, DNA may be extracted from blood.

7.9 Sample Storage and Destruction

Any blood or tissue samples collected according to the Schedule of Assessments (Table 2) 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 do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the solid tumor cancers (eg, mCRC, NSCLC, pancreatic cancer) with the dose response

and/or prediction of response to AMG 510, characterize antibody response, 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, biomarker development, 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.

Amgen or another third party manufacturer may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to investigational product(s) to investigate and further understand the NSCLC or CRC.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

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, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (**Section 7.1**) 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, adverse events, Subjects who have discontinued investigational product and/or 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. The investigator must document the level of follow-up that is agreed to by the subject.

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.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

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

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 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- subject request
- adverse event

- intolerance to AMG 510
- death
- lost to follow-up
- decision by Sponsor
- non-compliance
- requirement for alternative therapy
- disease progression as defined by **RECIST** 1.1 criteria (Appendix D) or disease progression accompanied by worsening of symptoms or deterioration of the subject's general condition.
- **p**regnancy
- [redacted]

8.3.2 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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition.

Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study, or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse 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 eCRF.

For situations when an adverse event or serious adverse event is due to non-small cell carcinoma of lung, colorectal cancer, or pancreatic adenocarcinoma 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.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in subject hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI) (see **Appendix F** for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through the safety follow-up visit are reported using 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),
- Severity and/or toxicity per protocol,
- Assessment of relatedness to investigational product and
- Action taken.

The adverse event grading scale used will be the CTCAE version 5.0. The grading scale used in this study is described in Appendix A The investigator must assess whether the adverse event is possibly related to AMG 510 [redacted] For each agent this relationship is indicated by a "yes" or "no" response to the questions: 'Is there a reasonable possibility that the event may have been caused by **investigational product**?' and [redacted]

The investigator must assess whether the adverse event is possibly related to any study mandated activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s) and/or procedure (including any screening procedure(s)). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s)), and/or procedure"?

The investigator is responsible for reviewing laboratory test results and determining 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.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the dosing interval of investigational product are recorded in the subject's medical record and are submitted to Amgen. Serious adverse events observed by the investigator or reported by the subject that occur after the safety follow-up visit through the end of the long-term follow-up period should be reported if there is a reasonable possibility that the event may have been caused by AMG 510. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form.

The investigator must assess whether the serious adverse event is possibly related to the investigational product. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product(s), and/or other protocol-required therapies? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records.

Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local regulatory requirements and procedures.

9.2.1.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge 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 for the purposes of expedited reporting.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking AMG 510 [redacted] report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur in a female subject through 37 days after the last dose of AMG 510 [redacted] or in a male subject's female partner through 97 days after the last dose of AMG 510 [redacted]. Female subjects who become pregnant while on study or within 37 days after receiving the last dose of study

drug will not receive subsequent scheduled doses and will be followed for safety until end-of-study visit.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through 37 days after the last dose of AMG 510 [redacted]

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested. If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Phase 1

10.1.1.1.1 Monotherapy (Parts 1a, 1b, and 2a)

10.1.1.1.1.1 Primary Endpoints:

- Safety: subject incidence of treatment-emergent adverse events, treatment-related adverse events, and clinically significant changes in vital signs, physical examinations, ECGs, and clinical laboratory tests
- Subject incidence of DLT

10.1.1.1.1.2 Secondary Endpoints:

- PK parameters of AMG 510 including, but not limited to C_{max}, time to achieve C_{max} (t_{max}), and AUC
- ORR, DOR, DCR, **PFS**, duration of stable disease**, and TTR** measured by CT or MRI and assessed per **RECIST** 1.1. Response will be assessed by independent radiologic review. Complete response and PR require confirmatory CT or MRI repeat assessment 4 weeks after the first detection of response.
- PK parameters of AMG 510 including, but not limited to, C_{max}, t_{max}, and AUC in the fed and fasted state
- AMG 510 exposure/QTc interval relationship

10.1.1.1.1.3 Exploratory Endpoints:

- AMG 510 exposure/safety and exposure/efficacy relationships
- AMG 510 excretion in urine
- Characterization of potential metabolites of AMG 510 in plasma and urine, if appropriate
- **Pharmacodynamic changes observed in blood and/or biopsies if available**
- Quantification of biomarker expression at protein, RNA, and DNA levels, as appropriate
- Potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor tissue samples

[redacted]

[redacted]

[redacted]

10.1.1.2 Phase 2 (Monotherapy)

10.1.1.2.1 Primary Endpoint

- Objective response rate (ORR = CR + PR), measured by CT or MRI and assessed per **RECIST** 1.1. Response will be assessed by independent radiologic review. Complete response and PR require confirmatory CT or MRI repeat assessment 4 weeks after the first detection of response.

10.1.1.2.2 Secondary Endpoints

- DOR - defined as time from first evidence of confirmed PR or CR to disease progression or death due to any cause, whichever occurs first. Subjects without a duration ending event will be censored at their last evaluable disease assessment date. Progression will be based on an independent radiologic assessment of disease response per **RECIST** 1.1.
- DCR defined as CR + PR + stable disease rate measured as described for ORR.
- PFS - defined as time from first dose of AMG 510 until disease progression or death from any cause, whichever occurs first. Subjects who do not progress or die will be censored at their last evaluable disease assessment date. Progression will be on an independent radiologic assessment of disease response per **RECIST** 1.1.
- OS - defined as time from first dose of AMG 510 until death from any cause. Subjects who do not die will be censored at the date of last contact.
- PFS rate at 6 months and 12 months.
- OS rate at 12 months.
- Incidence and severity of adverse events.
- PK parameters of AMG 510 including, but not limited to, C_{max}, t_{max}, and AUC.
- **TTR - defined as time from first dose of AMG 510 until the first evidence of confirmed PR or CR.**

10.1.1.2.3 Exploratory Endpoints

- AMG 510 exposure/safety and exposure/efficacy relationships
- **Pharmacodynamic changes observed in blood and/or biopsies if available**
- Biomarkers of response and resistance to AMG 510 at the time of progression
  - Quantification of biomarker expression at protein, RNA, and DNA levels, as appropriate
  - Potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor tissue samples
- Changes in cancer-specific symptoms and overall health status using subject-reported outcome instruments:
  - Impact of treatment on disease-related symptoms and HRQOL (instruments; EORTC QLQ-C30 + disease-specific modules QLQ LC13 **and NSCLC SAQ** for NSCLC, and QLQ Pan 26 for pancreatic cancer)
  - Treatment-related symptoms and impact on the subject (**EORTC QLQ-C30,** selected questions from the PRO-CTCAE library and a single item about symptom bother**, item GP5 of the FACT-G**)
  - Physical function (instrument: EORTC QLQ-C30**, Physical function scale**)

10.1.2 Analysis Sets

10.1.2.1 Safety Analysis Set

The safety analysis set (SAS) will consist of all subjects who receive at least one dose of AMG 510. The analysis of all safety endpoints, unless noted otherwise, will be conducted on the SAS. For the phase 1 part of the study, the analysis of DLT will be restricted to DLT-evaluable subjects (see Section 3.3 for definition).

10.1.2.2 Pharmacokinetic Analysis Set

The PK Analysis Set will contain all subjects who have received at least 1 dose of the investigational product 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.

10.1.2.3 Phase 1 Monotherapy RP2D ORR Analysis Set

The phase 1 monotherapy RP2D ORR analysis set (P1OAS) will consist of all subjects with confirmed *KRASp.G12C* status whose initial dose of AMG 510 is at the RP2D and received at least 1 dose of AMG 510 in the phase 1 monotherapy dose exploration part, or the phase 1 monotherapy dose expansion part, and had at least 6-week response data. Subjects who stopped disease assessments prior to 6 weeks will be included in this analysis set if the data cutoff is at least 6 weeks after their first dose date. The futility and efficacy thresholds will be calculated for

monitoring the antitumor activity of monotherapy of AMG 510 during phase 1 expansion part using this analysis dataset.

10.1.2.4 Phase 2 Full Analysis Set

The phase 2 full analysis set (P2FAS) will consist of all phase 2 subjects who received at least 1 dose of AMG 510. The primary analysis (excluding the analysis of ORR) and the final analysis will be performed on the P2FAS.

10.1.2.5 Phase 2 ORR Analysis Set

The phase 2 ORR analysis set (P2OAS) will consist of all subjects in the phase 2 full analysis set who have had at least 6 weeks response data starting from day 1. Subjects who stopped disease assessments prior to 6 weeks will be included in this analysis set if the data cutoff is at least 6 weeks after their first dose date. The interim futility analysis and primary analysis of ORR will be performed on the P2OAS.

10.1.3 Covariates and Subgroups

10.1.3.1 Covariates

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

10.1.3.2 Subgroups

Subgroup analysis will be performed by tumor type. Other potential subgroups will be pre-specified in the statistical analysis plan.

10.2 Sample Size Considerations

10.2.1 Phase 1

Phase 1 part 1 – Dose Exploration: No more than 92 subjects will be enrolled in the dose exploration part of the study. Approximately 30 subjects enrolled in cohorts of n = 2-4 subjects (n = 4-8 at the highest planned dose level) will be used to estimate the monotherapy QD dosing MTD. [redacted] These sample sizes are based on practical considerations and are consistent with conventional oncology studies with the objective to estimate the MTD and to evaluate initial safety and tolerability. The probability of observing at least

1 DLT if the true DLT rate is 10 **to** 33% is provided in **Table** 8 for various number of subjects.

Table 8. Probability of Observing at Least 1 DLT

Number of Subjects	10% DLT Rate	33% DLT Rate
2	19	55
3	27	70
4	34	80
6	47	91
8	57	96
10	65	98
12	72	99

DLT = dose limiting toxicity

In order to better estimate the RP2D and to better characterize the safety, efficacy, PK, and pharmacodynamics for AMG 510 monotherapy, an additional 20 to 40 subjects may be enrolled to one or more monotherapy dose levels that have been shown to be safe and tolerable from which at least 6 subjects will be evaluated for food effect. The sample size of at least 6 subjects for food effect **assessment** is based on practical considerations and judged sufficient for the evaluation; no formal calculation was made.

Phase 1 part 2– Dose Expansion: **The maximum sample size in the dose expansion part to evaluate AMG 510 monotherapy is 60 in subjects with *KRAS p. G12C* mutant advanced solid tumor types. The actual sample size will depend on DLRT review with monitoring criteria defined in Section 10.4.1.2.** With 20 subjects receiving monotherapy AMG 510 in dose expansion, there is an 88% to 99% probability of observing at least 1 adverse event if the true event rate is 10% to 20% with 60 subjects there is a 45% to 95% probability of observing at least 1 adverse event if the true event rate is 1% to 5%.

The ORR will be reported by tumor types. For NSCLC, with 60 subjects, 95% of the times the true ORR will be between 0.188 and 0.432, when the observed ORR is 0.3; and when the true ORR is 0.3, the chance that the 95% CIs of ORR will be > 0.15 is 76%. For CRC, with 60 subjects, 95% of the times the true ORR will be between 0.108 and 0.323, when the observed ORR is 0.2; and when the true ORR is 0.2, the chance that the 95% CIs of ORR will be > 0.05 is 93%. Below table describes the scenarios with sample size of 20 to 60.

Table 9. Sample Size Justification

NSCLC		
Sample Size	95% Exact CI of the True ORR Given an Observed ORR = 0.3	Probability (ORR 95% CI Lower Bound > 0.15) Given True ORR = 0.3)
20	(0.119, 0.543)	39%
30	(0.147, 0.494)	41%
40	(0.166, 0.465)	56%
50	(0.179, 0.446)	67%
60	(0.188, 0.432)	76%
CRC		
Sample Size	95% Exact CI of the True ORR Given an Observed ORR = 0.2	Probability (ORR 95% CI Lower Bound > 0.05) given true ORR = 0.2)
20	(0.057, 0.437)	59%
30	(0.077, 0.386)	75%
40	(0.091, 0.356)	84%
50	(0.100, 0.337)	90%
60	(0.108, 0.323)	93%

ORR = objective response rate

[redacted]

10.2.2 Phase 2

The phase 2 part of the study will target an ORR over a benchmark rate to exclude based on the lower limit of the 95% CI for the observed ORR for each tumor type (NSCLC, CRC).

For NSCLC subjects, a large phase 3 trial (REVEL) for second-line treatment after disease progression on platinum-based therapy showed that an ORR of 23% was observed with ramucirumab plus docetaxel (Garon et al 2014, NCT01168973).

For CRC subjects, althouth the treatment for ≥ third line subjects with Regorafenib or TAS 102 has demonstrated ORR of only 1% to 4% (Li et al, 2015; Mayer et al, 2015; Grothey et al, 2013), these therapies has demonstrated survival

benefits. To justify the use of surrogate endpoint ORR in this phase 2 trial, a higher benchmark ORR for CRC is selected.

The benchmark ORR to exclude is selected as 23% for NSCLC and 10% for CRC. No benchmark ORR will be set for tumor types other than NSCLC and CRC because of low expected enrollment. A sample size of 105 subjects for NSCLC and 60 subjects for CRC will provide approximately a 90% probability that the lower limit of the ORR 95% CI exceeds the tumor-specific benchmark ORR.

The minimum observed ORRs that would exclude the benchmark ORR with 105 NSCLC subjects and 60 CRC subjects are 32% and 20%, respectively.

10.3 Adaptive Design

For phase 1 dose exploration, the adaptive features of the BLRM design are described in Appendix E. **For phase 1 dose expansion, the futility and efficacy thresholds are calculated and specified in Section 10.4.1.2.** For phase 2, futility analyses are described in Section 10.4.1.3.2**.**

10.4 Planned Analyses

10.4.1 Interim Analyses

10.4.1.1 Phase 1 (Part 1 - Dose Exploration)

Safety data will be reviewed on an ongoing basis by Amgen. Based on accumulating toxicity information, BLRM will be used to make dosing recommendations. After each cohort completes enrolment and after all DLT-evaluable subjects within the cohort have completed the DLT window, Amgen, in consultation with DLRT, will review the DLRM recommended dose level and will review all available cumulative data by cohort prior to making dose exploration decisions. As a sensitivity analysis, a one-parameter Continual Reassessment Method (CRM) model may be used to estimate the dose-toxicity relationship to help making dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and considered in all enrollment and dosing decisions.

The DLRT will be composed of the investigators, Amgen Medical Monitor, Amgen Global Safety Officer, 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 global safety officer, and all actively screening and enrolling investigators or their qualified sub-investigator designee. The team may recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), continuation or delay in dosing, repetition or expansion of a cohort, de-escalation to a lower dose, or termination of the study. The Amgen medical monitor and Global Safety Officer 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. All available study data including demographics, smoking status (prior and current), medical history, concomitant medications, AEs, 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 escalation/de-escalation decisions
- number of subjects per cohort
- continuation, delay or termination of dosing
- change of the dosing schedule
- termination of the study

10.4.1.2 Phase 1 (Part 2 - Dose Expansion)

This same DLRT will be responsible for reviewing data in the dose expansion phase to confirm the RP2D and determine the benefit/risk of proceeding to the phase 2 part of the study. The dose expansion part of the study (phase 1 - part 2) can open once an MTD or a RP2D and dosing schedule has been estimated in the dose exploration part of the study (phase 1 – part 1). If no DLT is observed in phase 1 – part 1, the RP2D will be estimated based on composite review of PK, overall safety/tolerability, and observed responses. Further confirmation of the RP2D dose will be sought in the phase 1 part 2 dose expansion.

In the dose expansion, additional subjects will be enrolled at the RP2D estimated in the phase 1 part 1 dose exploration. After a minimum of 20 subjects have been enrolled to the initial estimated monotherapy RP2D (including subjects enrolled to the RP2D in either the dose exploration [approximately 6] or the dose expansion [approximately 14] parts of the study) and have completed the 21-day DLT period, and after a minimum of

10 of these subjects have at least 6 weeks of response data (including all previous data from the dose expansion and backfill cohorts), the DLRT will review all available safety, laboratory, PK, and efficacy (physician assessment) data**.**

After **the** first review has been conducted, if a decision is made to continue to obtain additional data at the initial estimated RP2D prior to proceeding to phase 2, the intervals for subsequent reviews will be determined by the DLRT but should occur within a maximum of 20 additional subjects enrolled and dosed for 21 days. The maximum number of subjects that may be enrolled to the initial estimated RP2D in the monotherapy dose expansion group, without confirmation of this dose for phase 2, will not exceed 60. If another dose (or schedule) needs to be explored, additional subjects on that dose (or schedule), up to a total of 60, may be enrolled.

Based on emerging clinical efficacy data, the number of subjects with specific tumor types may be restricted/specified in the expansion part.

Antitumor activity will be monitored in terms of ORR by tumor types (NSCLC, CRC). Futility and efficacy thresholds will be calculated using Bayesian posterior probability approach based on the cumulative efficacy data and it will serve as a guidance to the DLRT. Enrollment will not be held to conduct this assessment.

Whenever DLRT will review the data, and there are at least 5 evaluable subjects in the tumor type, the futility and efficacy thresholds for that tumor type will be calculated using all the cumulative efficacy data in phase 1 Monotherapy RP2D ORR Analysis Set to provide the guidance. In the calculation of thresholds, a response is defined as either a confirmed or unconfirmed CR or PR as per RECIST 1.1.

10.4.1.2.1 Futility Thresholds

For NSCLC, the futility thresholds are calculated such that the Bayesian posterior probability of a true ORR ≤ 0.15 is > a high probability of 75%. For CRC, the futility thresholds are calculated such that the Bayesian posterior probability of a true ORR ≤ 0.05 is > than a high probability of 75%. A noninformative prior distribution of beta (1, 1) will be used.

NSCLC: probability (ORR ≤ 0.15) > 75%

CRC: probability (ORR ≤ 0.05) > 75%

10.4.1.2.2 Efficacy Thresholds

For NSCLC, the efficacy thresholds are calculated such that the Bayesian posterior probability of a true ORR > 0.25 is ≥ to a high probability of 60%. For CRC, the efficacy thresholds are calculated such that the Bayesian posterior probability of a true ORR > 0.1 is ≥ to a high probability of 60%. A noninformative prior distribution of beta (1, 1) will be used.

NSCLC: probability [ORR > 0.25] ≥ 60%

CRC: probability [ORR > 0.1] ≥ 60%

Table 10 and Table 11 are look up tables calculated for NSCLC and CRC, providing the detailed futility and efficacy thresholds with different numbers of response-evaluable subjects (having at least 6-week response data) when DLRT review the data. For example, at the time when DLRT plan to review the data, there are a total of 25 response-evaluable NSCLC subjects. If observing number of the response is ≤ 2, based on the table, the guidance will recommend not to continue due to the lack of efficacy. If observing number of the response is ≥ 7, the guidance will recommend continuing to phase 2. If the observing number of the response is in between and the total number of response-evaluable subjects at that RP2D has not reached the maximum 60, the guidance will recommend enrolling more patients in the phase 1 expansion cohort.

The operating characteristics of these thresholds are demonstrated assuming a minimal of 5 response-evaluable subjects per tumor type for the first DLRT review and every 5 response-evaluable subjects thereafter. The actual sample size per tumor type at each look will depend on tumor type distribution. Table 12 and Table 13 show the cumulative probabilities of recommending DLRT to stop the trial due to lack of efficacy and the cumulative probabilities of recommending DLRT to continue to phase 2 given the true ORR ranging from 0.1 to 0.5 for NSCLC subjects and 0.05 to 0.25 for CRC subjects.

Table 10. Look Up Table for NSCLC Subjects

Number of Subjects	Recommend Not to Continue if Observing the Number of Responses Below
5 ~ 7	Never stop for futility with this number of subjects
8 ~ 16	0
17 ~ 24	≤ 1
25 ~ 31	≤ 2
32 ~ 39	≤ 3
40 ~ 47	≤ 4
48 ~ 54	≤ 5
55 ~ 60	≤ 6
Number of Subjects	**Recommend Go to Phase 2 if Observing the Number of Responses below**
5 ~ 8	≥ 2
9 ~ 11	≥ 3
12 ~ 15	≥ 4
16 ~ 19	≥ 5
20 ~ 23	≥ 6
24 ~ 26	≥ 7
27 ~ 30	≥ 8
31 ~ 34	≥ 9
35 ~ 38	≥ 10
39 ~ 42	≥ 11
43 ~ 46	≥ 12
47 ~ 50	≥ 13
51 ~ 54	≥ 14
55 ~ 57	≥ 15
58 ~ 60	≥ 16

NSCLC = non-small cell lung carcinoma

Table 11. Look Up Table for CRC Subjects

Number of Subjects	Recommend Not to Continue if Observing the Number of Responses Below
5 ~ 26	Never stop for futility with this number of subjects
27 ~ 52	0
53 ~ 60	≤ 1
Number of Subjects	**Recommend Go to Phase 2 if Observing the Number of Responses Below**
5 ~ 12	≥ 1
13 ~ 21	≥ 2
22 ~ 31	≥ 3
32 ~ 40	≥ 4
41 ~ 49	≥ 5
50 ~ 59	≥ 6
60	≥ 7

CRC = colorectal cancer

Table 12. Cumulative Probability of Go/NoGo for NSCLC Subjects

Number of Subjects	True ORR					
	0.1		0.3		0.5	
	NoGo	Go	NoGo	Go	NoGo	Go
5	0%	8%	0%	47%	0%	81%
10	35%	11%	3%	67%	0%	96%
15	35%	13%	3%	77%	0%	99%
20	48%	13%	3%	79%	0%	99%
25	60%	13%	4%	83%	0%	100%
30	60%	13%	4%	85%	0%	100%
35	65%	13%	4%	86%	0%	100%
40	70%	13%	4%	87%	0%	100%
45	70%	13%	4%	89%	0%	100%
50	73%	13%	4%	90%	0%	100%
55	76%	13%	4%	90%	0%	100%
60	76%	13%	4%	91%	0%	100%

ORR = objective response rate.
Numbers are for demonstration purpose. The actual sample size per tumor type at each look will depend on tumor type distribution.

Table 13. Cumulative Probability of Go/No Go for CRC Subjects

Number of Subjects	True ORR					
	0.05		0.15		0.25	
	NoGo	Go	NoGo	Go	NoGo	Go
5	0%	23%	0%	56%	0%	76%
10	0%	40%	0%	80%	0%	94%
15	0%	41%	0%	84%	0%	96%
20	0%	45%	0%	89%	0%	99%
25	0%	46%	0%	91%	0%	99%
30	21%	47%	1%	93%	0%	100%
35	21%	48%	1%	94%	0%	100%
40	21%	48%	1%	95%	0%	100%
45	21%	48%	1%	96%	0%	100%
50	21%	48%	1%	96%	0%	100%
55	28%	49%	1%	96%	0%	100%
60	28%	49%	1%	96%	0%	100%

ORR = objective response rate.
Numbers are for demonstration purpose. The actual sample size per tumor type at each look will depend on tumor type distribution.

Based on emerging clinical efficacy data, the number of subjects with specific tumor types may be restricted/specified in the expansion part.

The DLRT may also recommend that additional subjects be enrolled at this estimated monotherapy RP2D or that a dose reduction or alternate dosing regimen be explored before proceeding to phase 2. The decision to proceed to the phase 2 monotherapy will be based on the totality of data from both exploration and expansion parts of the study.

A final estimate of the MTD and/or RP2D using BLRM will be evaluated and confirmed utilizing all DLT-evaluable subjects from the dose exploration and the dose expansion cohorts.

10.4.1.3 Phase 2

10.4.1.3.1 Safety

A data review team (DRT), internal to Amgen but external to the study team, will assess safety after approximately 30, 50, 70, and 100 subjects have been treated for 21 days. Based on their reviews, the DRT will make recommendations to Amgen regarding the continuation of the study. There will be no formal guidelines to stop for safety. The DRT will consist of 3 or more members including 2 or more clinicians with relevant specialties and 1 or more statisticians. The DRT will be supported by an independent statistician who is responsible for preparing reports that describe the ongoing clinical study data. Details regarding the responsibilities of the DRT and the independent statistician will be described in the DRT Charter.

10.4.1.3.2 Futility

The DRT will also oversee futility analyses performed by tumor type and based on the phase 2 ORR analysis set. The interim futility analyses will be conducted in a continuous manner using Bayesian predictive probability (Lee and Liu, 2008) for NSCLC and CRC separately. Interim futility analysis will be performed by tumor types (NSCLC, CRC). For NSCLC subjects, it will begin after approximately 25 response-evaluable subjects, defined as received at least 1 dose of AMG 510 and have had at least 6 weeks response data starting from day 1. For CRC subjects, it will begin after approximately 20 response-evaluable subjects. Subjects who stopped disease assessments prior to 6 weeks will be included in this analysis if the data cutoff is at least 6 weeks after their first dose date. Following this initial interim anlaysis, for each tumor type, subsequent interim analyses will be performed after every 10 subjects in each tumor type becomes response evaluable.

The Go criterion will be met if the probability that the true ORR exceeds the benchmark ORR is ≥ to a high probability of:

Go Criterion for NSCLC: probability [ORR > 0.23] ≥ 80%

Go Criterion for CRC: probability [ORR > 0.1] ≥ 95%

Given the existing observed data during the continuous monitoring stage, the Bayesian predictive probability is obtained by calculating the probability of reaching a Go Criterion should the treatment group be enrolled and evaluated to

the maximum planned final sample size of 105 NSCLC subjects and 60 CRC subjects. The Go criterion is for interim futility analysis purpose only.

Futility will be met if it is predicted that there is a small probability of reaching a Go Criterion upon full enrollment of 105 NSCLC subjects and 60 CRC subjects given the existing observed data. A noninformative prior distribution of beta (1, 1) will be used.

Futility NSCLS: Predictive probability of a Go decision < 5%

Futility CRC: Predictive probability of a Go decision < 30%

Further enrollment may be terminated if futility is met. The futility analyses will be based on site-assessed disease response and the futility rules will be nonbinding. Due to the efficacy already observed in NSCLC during dose escalation phase, there will be no enrollment pause for NSCLC during the futility analyses. Enrollment will be paused for CRC at the first interim futility analysis and may be paused at the subsequent interim analyses upon DRT's recommendation.

The decision rule and operating charateristics for continuous monitoring of ORR in NSCLC subjects and CRC subjects are provided in Table 14 and Table 15, respectively. For example, observing 3 or fewer observed responders after 25 NSCLC subjects have become evaluable would be considered futile due to a small probability of reaching a Go Criterion upon full enrollment of 105 subjects given the existing observed data.

Table 14. Stopping Boundary and Operating Characteristics in NSCLC Subjects

Number of Subjects	Considered Futile If Observing Number of Responses	Cumulative Probability of Futility					
		True ORR=0.1	True ORR=0.2	True ORR=0.3	True ORR=0.4	True ORR=0.5	True ORR=0.6
25	≤ 3	76%	23%	3%	0.2%	0.0%	0.0%
35	≤ 5	89%	32%	4%	0.3%	0.0%	0.0%
45	≤ 7	94%	39%	5%	0.3%	0.0%	0.0%
55	≤ 10	98%	51%	6%	0.3%	0.0%	0.0%
65	≤ 13	100%	63%	8%	0.3%	0.0%	0.0%
75	≤ 16	100%	73%	10%	0.3%	0.0%	0.0%
85	≤ 19	100%	80%	12%	0.4%	0.0%	0.0%
95	≤ 22	100%	85%	14%	0.4%	0.0%	0.0%
105	≤ 27	100%	94%	23%	0.5%	0.0%	0.0%
Average Number of Subjects		29	60	99	105	105	105

NSCLC = non-small cell lung carcinoma; ORR = objective response rate

Table 15. Stopping Boundary and Operating Characteristics in CRC Subjects

Number of Subjects	Considered Futile If Observing Number of Responses	Cumulative Probability of Futility					
		True ORR=0.05	True ORR=0.1	True ORR=0.15	True ORR=0.2	True ORR=0.25	True ORR=0.3
20	≤ 2	92%	68%	41%	20%	9%	4%
30	≤ 3	96%	75%	45%	23%	10%	4%
40	≤ 5	99%	85%	55%	27%	11%	4%
50	≤ 7	100%	92%	63%	32%	12%	4%
60	≤ 9	100%	95%	70%	35%	13%	4%
Average Number of Subjects		21	28	40	50	56	58

CRC = colorectal cancer; ORR = objective response rate

10.4.2 Primary Analysis

The primary analysis will occur **after** there are **at least 105** NSCLC evaluable subjects or **60** CRC evaluable subjects in the **phase 2 ORR** analysis set, whichever occurs first. **The data cutoff will be decided to allow sufficient time to demonstrate durability of ORR.** The data will be analyzed once they have been entered, cleaned, and locked.

The primary analysis will summarize **for** all tumor types even if it is triggered by **105** NSCLC subjects or **60** CRC subjects.

10.4.3 Additional Analysis Subsequent to Primary Analysis

If the primary analysis is triggered by **105** NSCLC (**60** CRC) subjects before **60** CRC (**105** NSCLC) subjects become evaluable, a subsequent analysis will occur when **60** CRC (**105** NSCLC) subjects become evaluable in the **phase 2** ORR analysis set. The data will be analyzed once they have been entered, cleaned, and locked.

10.4.4 Final Analysis

The final analysis will occur when the end of study as described in Section 3.4.2 has been reached. The data will be analyzed once they have been entered, cleaned, and locked. The purpose of this analysis is to summarize efficacy and safety after all subjects have complete follow-up.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Efficacy and safety analyses will pool together all tumor types and also present tumor types separately. In addition, safety analyses will be summarized by planned dose level and treatment (monotherapy or combination therapy).

Futility **and efficacy threshold in phase 1 and futility interim in phase 2** will be based on site-assessed disease response per **RECIST** 1.1. **P**rimary, final, and any additional efficacy analyses will be based on an independent radiologic assessment of disease response per **RECIST** 1.1.

Nominal 95% confidence intervals will be calculated.

10.5.2 Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	The percentage of subjects with an OR will be summarized along with a Clopper-Pearson exact confidence interval. Subjects without a post-baseline tumor assessment will be considered non-responders.
Secondary	DOR will be summarized with Kaplan-Meier quartiles and rates for select durations (eg, > 3, > 6, > 9, > 12 months). Disease control will be analyzed by the same methods used to analyze OR. OS will be summarized with Kaplan-Meier curves, quartiles, and rates for select timepoints (eg, 6 and 12 months). PFS will be summarized using the same methods as OS. **TTR will be summarized by the nonmissing sample size (n), mean, standard deviation, median, minimum, and maximum for responders**
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.5.3 Safety Analyses

Unless otherwise specified, analyses of safety endpoints will be done using subjects in the SAS, which includes subjects that are enrolled and received at least 1 dose of AMG 510. In addition, the analyses below apply to both the phase 1 and phase 2 portions of the study unless otherwise specified.

10.5.3.1 Dose Limiting Toxicity

Phase 1 Monotherapy: The number and subject incidence of DLTs will be tabulated by dose level. Subject incidence of DLTs will be used to fit the BLRM model to estimate the probability of having a DLT across dose levels; the median probability of a DLT and 95% credible interval will be reported (see Appendix E for details on BLRM model).

Phase 1 Combination Therapy: The number and subject incidence of DLTs will be tabulated by dose level.

10.5.3.2 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, and adverse events leading to withdrawal from investigational product or other protocol-required therapies will also be provided.

10.5.3.3 Clinical Laboratory Tests

Summaries of laboratory data over time and/or changes from baseline over time will be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided.

10.5.3.4 Vital Signs

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

10.5.3.5 Electrocardiograms

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QT interval corrected by Fridericia's formula 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.

10.5.3.6 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.

[redacted]

10.5.3.8 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug dictionary.

10.5.3.9 Other Analyses

Phase 1: The food-effect cohort PK parameter estimates will help assess the impact of food on the PK of AMG 510. The geometric means and 90% CI for the ratio of the geometric means (fed state/fasted state) will be estimated using a mixed effects model. The model will use the log-transformed PK parameters as the dependent variable (or response) and treatment conditions (fed versus fasted) as the independent variable. The median of t_{max} will be compared between fasted and fed conditions as well.

The relationship between AMG 510 exposure and QT/QTc interval changes will be inspected graphically and model-based PK/pharmacodynamic analyses may be conducted to examine the relationship further.

10.5.4 Pharmacokinetics Analysis

In phase 1, 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.

In phase 2, for AMG 510, PK parameters (eg, C_{max}, t_{max} and AUC) will be determined where possible. 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.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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 template are to be communicated formally in writing from the Amgen Study Manager to the investigator. The written **ICF** is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any investigational product(s) is/ are administered. A legally acceptable representative is 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.

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. 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. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed ICF is to be provided to the subject or legally acceptable 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.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. 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.

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 is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for 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.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the 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 date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in strict confidence by the investigator, except as described below.

In compliance with governmental/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 named such individuals to have access to his/her study related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center 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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, the Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB/IEC must be informed of all amendments and give approval. 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.

Amgen reserves the right to terminate the study at any time. 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 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 it is available commercially.

12.2 Study Documentation and Archive

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 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. **The CRF is the source document for ethnic origin.**

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 CRF, 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 (POR), 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.

12.3 Study Monitoring and Data Collection

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.

The Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the CRFs.

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.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing 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.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 2 through Table 6), 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.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

12.6 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should 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 should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should 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 should qualify for authorship, and all those who qualify should be listed.
- Each author should 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 corporate review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 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.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE **version 5.0**) is available at the following location:

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

Appendix B. Sample Serious Adverse Event 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.

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.

Protocol specified hospitalizations are exempt.

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

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.
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 # 20170543
AMG 510

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

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

3. SERIOUS ADVERSE EVENT

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

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?								Outcome of Event 1-Resolved 2-Not resolved 3-Fatal 4-Unknown	Check only if event is related to study procedure eg, biopsy
						AMG510		pembrolizumab		<Device>		<Device>			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	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

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 510	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
pembrolizumab	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____

AMGEN Study # 20170543 AMG 510	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

								☐ Unavailable / Unknown

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20170543 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.		

Appendix C. Pregnancy and Lactation Notification Worksheets

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: 20170543

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (___)_____ Email _____

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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

AMGEN 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: 20170543

Study Design: [X] Interventional [ ] Observational (If Observational: [ ] Prospective [ ] Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

Did the subject withdraw from the study? [ ] Yes [ ] No

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: [ ] Female [ ] Male

Is the infant healthy? [ ] Yes [ ] No [ ] Unknown [ ] N/A

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Appendix D. Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

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 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 two 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 IV contrast as well as timing of scanning. CT 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 five (5) lesions per organ and ten (10) 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 case report form (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 one 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 lesion(s) or/and maintenance of tumor marker level above the normal limits.
* Progressive Disease (PD):	Unequivocal progression of existing non-target lesions and/or appearance of one or more new lesions.[1]

[1] 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 one 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 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

NE = Not evaluable

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‡
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

‡ "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[†]
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

[†] 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 the 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 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 then 5mm 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 complete response (CR) depends on this determination, it is recommended that the residual lesion be further investigated by fluorodeoxyglucose-positron emission tomography (**FDG-**PET) or PET/computed tomography (**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 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 progressive disease 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.

Appendix E. Two-parameter BLRM Design

A two-parameter Bayesian logistic regression model (BLRM, Neuenschwander et al, 2008) is used to guide dose escalation. The maximum tolerated dose (MTD) target Toxicity Probability Interval (TPI) for dose limiting toxicity (DLT) is (0.20, 0.33) and a TPI of (0.33, 1.00) is defined as excessive. The design seeks to identify a dose most likely to have a DLT rate in the target TPI, but with overdose control that limits the possibility the dose has an excessive DLT rate (Babb et al, 1998). The probability of a DLT at dose level d_i is assumed to follow a Bernoulli distribution with probability p_i where the logit of p_i increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

$$\log [p_i / (1-p_i)] = \text{logit}(p_i) = \log[a] + \exp(\log[b]) \log (d_i / d_{ref})$$

where a and b are random variables and d_{ref} is one of the planned dose selected as the reference dose.

A bi-variate normal prior distribution (Neuenschwander et al, 2008) was selected for theta = (log a, log b) where the probability that the true DLT rate is ≤ 0.40 at 180 milligrams (mg) is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose (720 mg) is 0.05. Additionally, the prior is such that p_i is approximately 0.05 for the 180 mg dose and 0.25 for the reference dose.

The operating characteristics of the two-parameter BLRM design were evaluated via simulation. The cohort size was fixed to 2 or 4 subjects. The initial dose level is 180 mg and subsequent doses were selected based on the following rules:

- After each cohort, the next dose is the one with the highest probability of the target TPI, but with a less than 0.25 probability of an excessive TPI.
- Escalation to a dose level that is greater than 2x the current dose level is not allowed.

Dose escalation was stopped given 1 or more of the following conditions:

- There have been at least 6 subjects treated at the dose recommended by the model.
- A maximum number of 30 subjects are evaluated. Operating characteristics are described below.

Operating characteristics

A total of 4 planned dose levels (unit: mg) were considered: 180, 360, 720 and 960. Two intermediate dose levels were also considered: 270 and 540 mg. The design was evaluated for 4 possible dose-response scenarios: Low MTD, Mid MTD, High MTD and

a scenario where none of the planned dose levels are tolerable. Table 16 shows the dose level and true probability of DLT for each scenario used in the simulated studies estimating the MTD. Table 17 reports the operating characteristics from 1000 simulated studies estimating the MTD when the target TPI is (0.20, 0.33). The rate of MTD selected and the number of subjects assigned to each dose level are presented in Table 18.

Table 16. True Probability of DLT by Scenario for Simulated Studies Estimating MTD

Dose Level	180	270	360	540	720	960
MTD Scenario						
High	0.01	0.01	0.05	0.15	0.25	0.33
Mid	0.05	0.15	0.25	0.33	0.43	0.53
Low	0.15	0.25	0.33	0.43	0.53	0.63
No tolerable dose levels	0.35	0.43	0.50	0.58	0.65	0.73

DLT = dose-limiting toxicity; MTD = maximum tolerated dose

Table 17. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD When the Target TPI is (0.20, 0.33)

MTD Scenario	High		Mid		Low		No tolerable dose levels	
Subjects per cohort	4	2	4	2	4	2	4	2
Number of Subjects Median (IQR)	20 (16 to 24)	12 (12 to 14)	20 (16 to 24)	12 (10 to 14)	16 (12 to 20)	10 (2 to 14)	8 (4 to 12)	2 (2 to 8)
Number of DLTs Median (IQR)	2 (2 to 4)	2 (1 to 2)	4 (3 to 5)	3 (2 to 3)	4 (3 to 6)	2 (1 to 4)	3 (2 to 4)	2 (1 to 3)
Proportion of DLT (%) Median (IQR)	12.5 (10 to 17)	14.3 (8 to 19)	25.0 (19 to 25)	25.0 (19 to 35)	26.7 (25 to 37)	37.5 (25 to 50)	50.0 (37 to 50)	50.0 (43 to 50)
Percentage of studies recommending dose with DLT probability of:								
≤ 10%	4.6	9.2	11.2	25.9	29.7*	53.6*	82.3*	89.3*
> 10% and ≤ 20%	47.2	55.6	4.6	2.0	10.3	0.9	NA	NA
> 20% and ≤ 33%	48.2	35.2	78.2	64.3	47.5	30.3	NA	NA
> 33%	NA	NA	6.0	7.8	12.5	15.2	17.7	10.7
Probability of identifying MTD to have 15% to 33% DLT probability	95.4	90.8	82.8	66.3	57.8	31.2	NA	NA

DLT = dose-limiting toxicity; IQR = interquartile range; MTD = maximum tolerated dose; TPI = toxicity probability interval; NA=not applicable
* In the low MTD scenario and the scenario where all planned dose levels are intolerable, this represents the percent of studies declaring all planned dose levels as not tolerable.

Table 18. Rate of MTD Selected and Number of Subjects Assigned at Each Dose Level by Scenario

MTD Scenario	High		Mid		Low		No tolerable dose levels	
Number of Subjects Per Cohort	4	2	4	2	4	2	4	2
Rate of MTD selected at each dose level (%):								
Below lowest dose	0.2	2.6	8.1	25.0	29.7	53.6	82.3	89.3
180 mg	0.1	0.0	3.1	0.9	10.3	0.9	9.2	0.9
270 mg	0.0	0.0	4.6	2.0	9.0	2.2	3.2	1.0
360 mg	4.3	6.6	43.8	31.3	38.5	28.1	4.7	7.4
540 mg	47.2	55.6	34.4	33.0	10.8	14.3	0.5	1.4
720 mg	44.3	33.2	5.2	7.8	1.6	0.9	0.1	0.0
960 mg	3.9	2.0	0.8	0.0	0.1	0.0	0.0	0.0
Average number of subjects at each dose level								
180 mg	4.1	2.0	4.7	2.3	5.3	2.4	5.1	2.4
270 mg	0.2	0.2	1.6	0.8	2.1	0.9	1.4	0.5
360 mg	4.3	2.5	6.0	3.5	5.1	3.1	1.6	1.7
540 mg	5.3	4.3	4.7	3.2	2.6	1.9	0.3	0.6
720 mg	5.6	3.3	1.8	1.4	0.7	0.5	0.1	0.1
960 mg	0.5	0.2	0.2	0.0	0.1	0.0	0.0	0.0

MTD = maximum tolerated dose.

Operating Characteristics for Standard 3+3 Design

As a comparison, the operating characteristics from 1000 simulated studies estimating the MTD when using a standard 3+3 design are reported in Table 19.

Table 19. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD Using a 3+3 Design

MTD Scenario	High	Mid	Low	No tolerable dose levels
Number of Subjects	15	12	12	6
Median (IQR)	(12 to 18)	(12 to 15)	(9 to 13)	(3 to 12)
Number of DLTs	2	3	3	3
Median (IQR)	(2 to 3)	(2 to 4)	(2 to 4)	(2 to 3)
Proportion of DLT (%)	16.7	23.8	26.7	33.3
Median (IQR)	(11 to 20)	(20 to 27)	(22 to 33)	(33 to 67)
Percentage of studies recommending dose with DLT probability of:				
≤ 10%	44.7	43.5	19.4*	65.9*
> 10% and ≤ 20%	0.0	0.0	47.4	NA
> 20% and ≤ 33%	55.3	43.3	29.5	NA
> 33%	NA	13.2	3.7	34.1
Probability of identifying MTD to have 15% to 33% DLT probability	55.3	43.3	76.9	NA

DLT = dose-limiting toxicity; IQR = interquartile range; MTD = maximum tolerated dose; NA=not applicable
* In the low MTD scenario and the scenario where all planned dose levels are intolerable, this represents the percent of studies declaring all planned dose levels as not tolerable.

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

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

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

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

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

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin 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 the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 20. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

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

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

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

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

If signs or symptoms recur with rechallenge, then [Amgen investigational product and other protocol-required therapies, as appropriate] is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 20) 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 Case Report Form (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 9.1.2.

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 20 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.

Summary of Changes Protocol Amendment 1 to Amendment 3

Protocol Title: A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 Monotherapy in Subjects With Advanced Solid Tumors With *KRAS p.G12C* Mutation and AMG 510 Combination Therapy in Subjects With Advanced NSCLC With *KRAS p.G12C* Mutation

Amgen Protocol Number (AMG 510) 20170543

EudraCT Number 2018-001400-11

NCT Number NCT03600883

Amendment Dates: 28 March 2019 and 22 May 2019

Rationale for Protocol Amendment 1 to Superseding Protocol Amendment 2:

The main change for Protocol Amendment 2 is the addition of the phase 2 portion of the study. The ongoing phase 1 portion was also amended as described below.

The protocol is being amended to incorporate changes in the study design as follows:

Overall, the addition of the phase 2 and the updates to the ongoing phase 1 portion of the study required updates across multiple sections of protocol including but not limited to the following: Protocol Synopsis, Study Schemas, Objectives and Endpoints (Section 1.0), Hypothesis (Section 2.7), Experimental Plan (Section 3.0), Subject Eligibility (Section 4.0), Treatment Procedures (Section 7.0), Schedule of Assessments (Section 7.1), Study Procedures (Section 7.2) and Statistical Considerations (Section 10). The first in human (FIH) portion of the study will continue as planned and in the protocol is noted as the Phase 1 portion.

Phase 2:

- Phase 2 is a multicenter, non-randomized, open-label study to evaluate efficacy and safety/tolerability of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors (NSCLC, CRC, and other tumors)

Updates to Phase 1:

- A phase 1, BID cohort was added to evaluate initial safety, PK and pharmacodynamics of AMG 510

- [redacted]
- Modify the phase 1 dose expansion cohort (part 2a) to allow enrollment of subjects with any tumor type into 1 cohort of up to 60 subjects
- Clarify that the backfill enrollment in phase 1 part 1a will be expanded up to 40 subjects
- Add details on the subjects being enrolled in the phase 1 part 1a portion of the study at sites in Japan

Additional changes to the protocol include:

- Update the number sites that will be included in the study
- Update RECIST text to align with the RECIST templated language.
- Removal of self-evident corrections language
- Administration, typographical, and formatting changes were made throughout the protocol

Rationale for Superseding Protocol Amendment 2 to Protocol Amendment 3:

The protocol is being amended to incorporate following key changes in the study design based on the feedback received from the regulatory agency on protocol amendment 2:

Updates to Phase 1:

- Sample size justification is provided for enrollment up to 60 subjects in phase 1 expansion portion.
- Futility/efficacy thresholds are added to monitor antitumor activities in phase 1 expansion to provide guidance to DLRM for determining RP2D and continuing to phase 2.
- Revision to use standard RECIST 1.1 for analysis of tumor response.

Updates to Phase 2:

- Revised patient population for NSCLC and CRC as defined by the eligibility criteria in terms of the extent of prior therapies.
- Clarified that twice-daily dosing cohort (phase 1 part 1b) will only be initiated after completion of preliminary food effect evaluation.
- Sample sizes for NSCLC, CRC are adjusted based on new benchmark rates
  - For NSCLC, revised the benchmark rate to 23% to exclude from the lower limit of the 95% confidence interval for observed ORR.
  - For CRC, revised the benchmark rate to 10% to exclude from the lower limit of the 95% confidence interval for observed ORR.

- Clarified that efficacy analysis will be performed using only “Phase 2” portion. Language pertaining to pooling subjects at RP2D from phase 1 and phase 2 for efficacy analysis is removed.
- Removed interim analysis for efficacy.
- Futility interim analysis in phase 2 portion is updated to allow continuous monitoring using Bayesian predictive probability method.
- Revision to use standard RECIST 1.1 for analysis of tumor response.
- Additional changes were made to the protocol with the following rationales.
- Time to response was added as an secondary endpoint in all phases to describe timing aspect of AMG 510 response profile.
- Removed the inclusion criteria requirement for alkaline phosphatase . Alkaline phosphatase (ALP) is often elevated in advance solid tumor with bone or liver metastasis and may not reflect liver function required to participate in the clinical trial when other liver function parameter criteria (AST, ALT, INR, Bilirubin) are met.
- Clarification of the inclusion criteria 215 pertaining birth control methods in accordance to Clinical Trial Facilitation and Coordination Gropu (CTFG) guidance.
- [redacted]
- Additional patient-reported outcomes (NSCLC SAQ and GP5 FACT-G) were added to fully understand the impact of treatment on patients from their perspective.
- Addition of urine pregnancy test on day 1 of every cycle in female subjects with child bearing potential to meet CTFG guidance related to pregnancy testing in clinical trials.

Statistical Analysis Plan

Protocol Title:	A Phase 1, First-in-Human, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 in Subjects with Advanced Solid Tumors with a Specific KRAS Mutation
Short Protocol Title:	AMG 510
Protocol Number:	20170543
NCT Number:	NCT03600883
Authors:	[redacted]
Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320 Phone: +1 805-447-1000
SAP Date:	**Document Version** — **Date** **Original (v 1.0)** — 14 November 2018

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ANC	Absolute neutrophil count
AUC	Area under the concentration-time curve
ALK	Anaplastic lymphoma kinase
BCRP	Breast cancer resistance protein
BLRM	Bayesian Logistic Regression Model
C_{max}	Maximum observed concentration
CR	Complete response
CRC	Colorectal cancer
CT	Computed tomography
CYP3A	Cytochrome P450 3A
DDI	Drug-drug interaction
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DILI	Drug induced liver injury
DOR	Duration of response
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
End of Study	Defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Follow-up	Defined as when the last subject completes the last protocol-specified assessment in the study
End of Treatment	Defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
Exposure-Response Analysis	Mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic [PK] exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamics effects, efficacy and safety endpoints
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FIH	First-in-human
HepBsAg	Hepatitis B surface antigen

Abbreviation or Term	Definition/Explanation
HepCAb	Hepatitis C antibody
HNSTD	Highest non-severely toxic dose
ICF	Informed consent form
ICH	International Conference of Harmonization
IVD	In vitro diagnostic
IR	Immediate-release
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
KRASG12C	KRAS protein with a G12C mutation at the protein level
KRAS p.G12C	KRAS DNA with a mutation resulting in a G12C mutation at the protein level
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NOEL	No observed effect level
NRAS	Neuroblastoma RAS viral oncogene homolog
NSCLC	Non-small-cell lung carcinoma
ORR	Objective response rate
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed death-ligand 1
P-gp	P-glycoprotein
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PO	Oral(ly)
PFS	Progression-free survival
PR	Partial response
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
QD	Once daily
QTc	Corrected QT (interval)
RAS	Rat sarcoma viral oncogene homolog
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 Dose

Abbreviation or Term	Definition/Explanation
SD	Stable disease
STD10	Severely toxic dose in 10% of animals
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
Study Day 1	Defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
t_{max}	Time to reach maximum concentration
TGI	Tumor growth inhibition
VEGF	Vascular endothelial growth factor

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within Amendment 1 of the protocol for study 20170543, AMG 510 dated 12 July 2018. The scope of this plan includes the interim analysis, the primary analysis and the final that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of AMG 510 in adult subjects with KRAS p.G12C mutant solid tumors & Estimate the maximum tolerated dose (MTD) and/or a biologically active dose	• Safety: subject incidence of dose limiting toxicity (DLTs), treatment-emergent adverse events, treatment-related adverse events, and clinically significant changes in vital signs, physical examinations, electrocardiogram (ECGs), and clinical laboratory tests
Secondary	
• Characterize the pharmacokinetics (PK) of AMG 510 following administration as an oral tablet formulation	• 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)
• To evaluate tumor response assessed by CT or MRI using RECIST 1.1 criteria of AMG 510 as monotherapy in subsets of solid tumors with KRAS p.G12C mutation	• Objective response rate (ORR), duration of overall response (DOR), overall survival (OR), progression-free survival (PFS), and duration of stable disease measured by CT or MRI and assessed per RECIST 1.1 criteria
• To evaluate the effect of food on the oral pharmacokinetics of AMG 510	• PK parameters of AMG 510 including, but not limited to, C_{max}, t_{max}, and AUC in the fed and fasted states for the food effect assessment

Objectives	Endpoints
Secondary (Continued)	
• To evaluate the relationship between changes in QTc and AMG 510 exposure	• AMG 510 exposure/QTc interval relationship
Exploratory	
• To explore pharmacokinetic/ pharmacodynamic relationships for safety and/or efficacy endpoints	• AMG 510 exposure/safety and exposure/efficacy relationships
• To characterize AMG 510 excretion in urine	• AMG 510 excretion in urine
• To identify metabolites of AMG 510 in plasma and urine	• Characterization of potential metabolites of AMG 510 in plasma and urine, if appropriate
• To investigate potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor samples.	• Quantification of biomarker expression at protein, RNA, and DNA levels, as appropriate • Potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor samples

2.2 Hypotheses and/or Estimations

At least 1 dose level of AMG 510, in repeat oral administrations, will achieve acceptable safety and tolerability in subjects with advanced *KRAS p.G12C* mutant solid tumors, with evidence of anti-tumor activity.

3. Study Overview

3.1 Study Design

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study to evaluate safety and tolerability of AMG 510 in subjects with advanced *KRAS p.G12C* mutant solid tumors. AMG 510 will be evaluated as an oral therapeutic. The study will be conducted in 2 parts: Part 1 – Dose Exploration and Part 2 – Dose Expansion.

Part 1 is aimed at evaluating the safety, tolerability, PK and pharmacodynamics of AMG 510 and determining the MTD of repeat daily (QD) dosing schedule in subjects with advanced *KRAS p.G12C* mutant solid tumors using a Bayesian Logistic Regression Model (BLRM) design.

Part 2, the dose expansion part of the study, can open once the MTD and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) has been determined in Part 1. The dose exploration part of the study will consist of approximately 50 subjects and the dose expansion part will consist of approximately 60 additional subjects, including at least 3 groups with specific tumors harboring *KRAS p.G12C* mutations (non-small cell lung cancer [NSCLC], colorectal cancer [CRC], and all other solid tumors). Different schedules can be used in the dose expansion part based on clinical and PK data from all parts of the dose exploration. The DLT evaluation period will be 21 days. Based on emerging clinical efficacy data, the groups explored in the expansion part can be modified.

Dose Exploration – Part 1

Dose exploration cohorts will estimate the safety, tolerability, PK, and pharmacodynamics of different doses of AMG 510 in subjects with advanced *KRAS p.G12C* mutant solid tumors. Subjects will receive AMG 510 daily administered orally. Enrollment into the dose exploration cohorts may be from any eligible solid tumor type. Dose escalation will begin with 2-4 subjects treated at the lowest planned dose level of 180 mg. Dose escalation will follow the planned Study Schema schedule with 2-4 subjects treated in each cohort. If no DLT is observed, dose escalation will continue to the next planned dose cohort as per Study Schema. Once a subject experience a DLT, dosing for subsequent cohorts will be recommended using the dose level recommendation from the Bayesian Logistic Regression Model (BLRM). The decision to advance to the next dose level will be recommended by the Dose Level Review Team (DLRT) using the dose level recommendation from BLRM, as appropriate, and by evaluating available safety data, laboratory, and PK information.

Intra-subject dose escalations are allowed on this study. Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle once the next dose cohort has been deemed safe by the DLRT and after consultation with the sponsor if:

- no DLT has been reported for this subject during or after completion of the DLT period
- the subject has not experienced any ≥ grade 2 adverse events (deemed treatment related by the investigator) during treatment

Subjects who do not proceed to a higher dose may receive extra cycles at the original dose.

Dose exploration will continue until any of the following events.

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 DLT-evaluable subjects)
- The MTD is identified, BLRM recommends a dose level which already has 6 DLT-evaluable subjects

Additional subjects (up to 20) may be enrolled in one or more dose levels that have been shown to be safe and tolerable, defined as backfill enrollment. This backfill enrollment will be done to better estimate the RP2D and better characterize the safety, efficacy and pharmacodynamics for AMG 510 and may be concurrent with dose escalation to identify the MTD. Additionally, food effect evaluation will be conducted in at least 6 subjects from backfill enrollment in cycle 2 or later.

Dose Expansion – Part 2

Upon completing the dose exploration part of the study and depending on data obtained, dose expansion may proceed with three groups consisting of subjects with KRAS p.G12C mutant solid tumors:

- Group 1 (NSCLC) - subjects with advanced KRAS p.G12C mutant NSCLC
- Group 2 (CRC) - subjects with advanced KRAS p.G12C mutant CRC
- Group 3 (Other) - subjects with advanced KRAS p.G12C mutant solid tumor types other than the tumor types specified in Groups 1 and 2

Figure 1. Study Design and Treatment

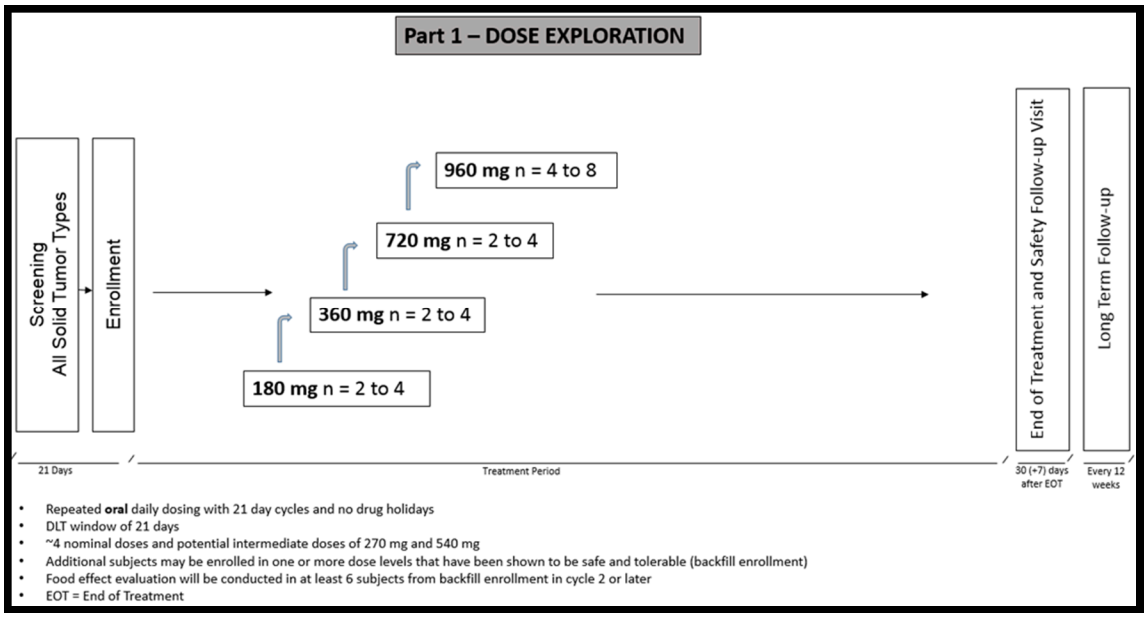


Figure 2. Study Design and Treatment

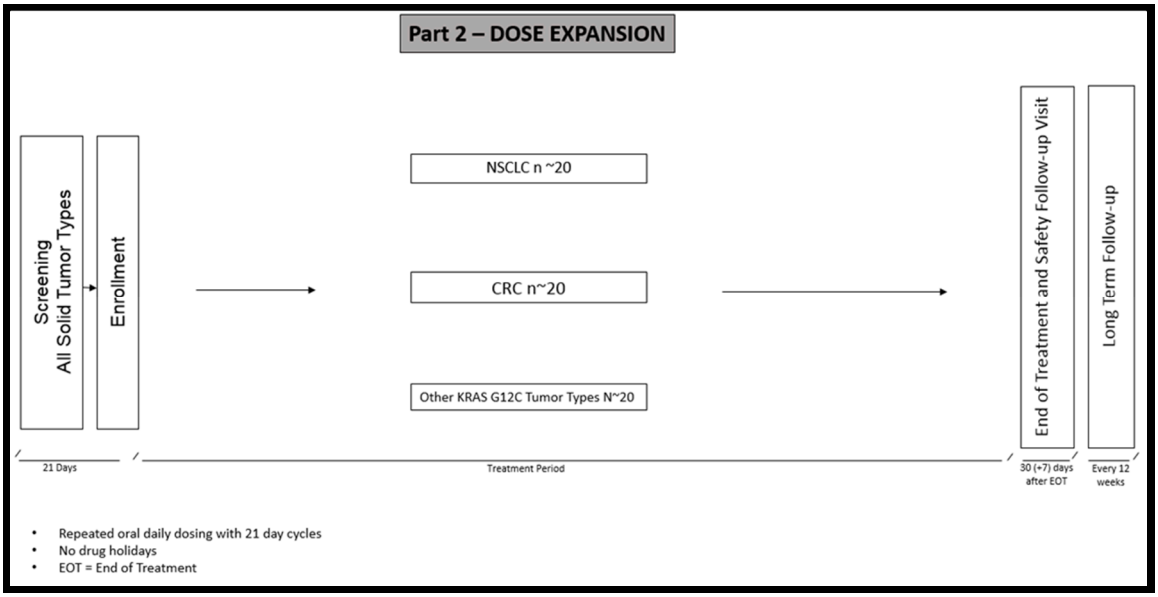
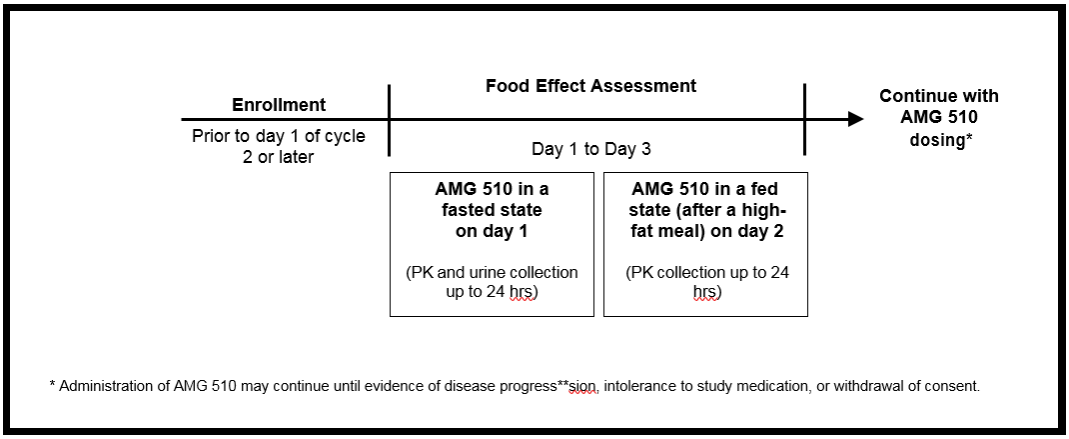


Figure 3. Food Effect Assessment



3.2 Sample Size

Part 1 – Dose Exploration:

No more than 50 subjects will be enrolled to the dose escalation cohorts. Approximately 30 subjects will be needed to estimate the MTD.

An additional 20 subjects may be enrolled by backfill enrollment from which at least 6 subjects will be evaluated for food effect.

Part 2 – Dose Expansion:

Approximately 60 subjects will be enrolled in the dose expansion part of the study, which will be conducted in at least 3 groups.

- Group 1: up to 20 subjects with advanced KRAS G12C mutant NSCLC.
- Group 2: up to 20 subjects with advanced KRAS G12C mutant CRC.
- Group 3: up to 20 subjects with advanced KRAS G12C mutant solid tumor types other than specified in Groups 1 and 2.

3.3 Adaptive Design

A two-parameter Bayesian Logistic Regression Model (BLRM, Neuenschwander et al, 2008) is used to guide dose escalation.

Details of the adaptive BLRM design are described in the Protocol Appendix E

4. Covariates and Subgroups

4.1 Planned Covariates

The following baseline covariates may be used to evaluate efficacy endpoints in subgroups or in multivariate analysis: Age at baseline (< 65, >= 65 years), prior lines of anti-cancer therapy (1, 2, > 2) and ECOG performance status.

4.2 Subgroups

Biomarker data may be incorporated in additional exploratory subgroup or multivariate analyses. The analyses of biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoints.

5. Definitions

Adverse Event (AE):

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.

The definition of adverse events includes worsening of a preexisting medical condition. A preexisting condition that has not worsened during the study, or involves an intervention, is not considered an adverse event.

Age at Enrollment:

Subject age at enrollment will be determined using the age in years reported in the clinical database.

AUC:

The area under the plasma drug concentration-time curve (AUC) reflects the actual body exposure to drug after administration of a dose of the drug.

Baseline:

For any variable, unless otherwise specified the baseline is the last assessment taken prior to the first administration of AMG 510. For parameters/assessments not scheduled to be performed (or scheduled but not performed) on the same day as the first administration of AMG 510, the baseline value is the value from the screening period measured closest to the day of first administration of AMG 510.

Baseline ECG Values in Triplicate:

The mean of values in a triplicate should be calculated for Baseline. For all post-baseline ECG, the mean value for measurements taken at the same assessment will be calculated and used in the analysis.

When an ECG is missing within a triplicate, all available data will be averaged for that time point.

Best Overall Response (BOR):

Best overall response (BOR) for a subject is the best observed post baseline disease response. Overall response assessments occurring after the start of the first subsequent anticancer therapy will not be included. The investigator reported response information collected on the CRF will be used to determine the response. No additional derivations will be required to classify the response.

BOR is defined as the best response in the following order: CR, PR, SD, PD, or NE, where CR and PR require confirmation by a repeat, consecutive scan at least 4 weeks after the first documentation of response.

Please refer Protocol Appendix D for more details.

Body Mass Index (BMI):

Body Mass Index should be calculated using the following formula:

$BMI\ (kg/m^2) = weight\ (kg) / [height\ (cm)/100]^2$

Body Surface Area (BSA):

The Body Surface Area should be calculated using the following formula:

$BSA = 0.007184 \times weight(kg)^{0.425} \times height(cm)^{0.725}$

C_{max}:

Maximum observed drug concentration.

Change From Baseline:

Change from Baseline is the arithmetic difference between post-dose assessments and Baseline value.

Change (absolute) from Baseline = (Post-baseline Value – Baseline Value)

Change (percent) from Baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

Dose Limiting Toxicity (DLT):

Dose-limiting toxicity (DLT) is defined as AMG 510-related toxicity with an onset within the first 21 days following first dose with the criteria defined in section 6.1.1.2.1 of the Protocol.

Disease control rate (DCR):

DCR is defined as the proportion of patients in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD) > 6 months.

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 that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study) or death in the absence of progression.

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

DOR includes those subjects who have confirmed overall response.

Subjects who maintain their objective response, whether on-study or lost to follow-up, will be censored on date of last contact.

Duration of stable disease:

Duration of stable disease will be measured from the start of treatment until the earlier of time criteria for progression are met or death in the absence of progression.

If the subject hasn't met the criteria for progression during the study, then the subject will be censored at last evaluable tumor assessment date.

End of Follow-Up:

It is defined as when the last subject completes the last protocol-specified assessment in the study.

End of IP administration (End of IP Admin):

End of IP Admin for each subject is defined as the date the decision was made to end IP as recorded on the End of Investigational Product Administration CRF page.

End of Study (Individual Subject):

End of study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study CRF page.

End of Study (Primary Completion):

It is defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s).

End of Study (End of Trial):

It is defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts.

End of Treatment:

It is defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject.

Fridericia-corrected QT Interval (QTcF):

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows:

$$QTcF=QT/(RR/1000)^{1/3}$$

Investigational Product:

The term 'investigational product' is used in reference to AMG 510.

Last Investigational Product Dose Date:

The last IP date for each subject is defined as the latest date IP administered.

Long Term Follow-Up:

Following the SFU visit, there will be a LTFU period for clinical evaluation of disease status and survival. Subjects will be followed via telephone every 12 weeks (± 2 weeks) for assessment of survival and documentation of anti-cancer treatment. Subjects will be followed for a maximum of 2 years from the first dose of AMG 510, or until subject death, whichever occurs first.

Subjects will allow Amgen continued access to medical records so that information related to subjects' health condition, including disease status and survival, may be obtained.

Maximum Tolerated Dose (MTD):

A final estimate of the MTD will be made based on a Bayesian Logistic Regression Model (BLRM) utilizing all DLT-evaluable subjects from the dose exploration and dose expansion cohorts. Based on the BLRM, the MTD is defined as the dose with the highest probability of a DLT rate between the targeted toxicity (0.2, 0.33) interval while controlling the probability of excessive and unacceptable toxicity below 25%. The MTD will estimated separately by dosing regimen if multiple regimens are evaluated.

Objective Response Rate (ORR):

Objective response rate is defined as the proportion of patients with a BOR of CR or PR.

Overall survival (OS):

Overall survival (OS) is defined as the time from treatment start with AMG 510 until event of death due to any cause. Subjects without event will be censored at their last contact date.

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.

Progression Free-Survival (PFS):

The PFS is defined as interval between the date of first dose of AMG 510 and the date of disease progression or death due to any cause (whichever comes first).

Subjects who are alive and have not progressed, whether on-study or lost to follow-up, will be censored at their last evaluable tumor assessment date.

Relative Dose Intensity for First Cycle:

Relative DI will be calculating by using the below formula for first cycle as follows:

RDI = [non-missing (dose*days) / planned (dose*days)] *100

Safety Follow-Up:

It is defined as the subject visit up to 30 (+7) days after last dose of AMG 510 is received.

Study Day:

Post-study day: study day= (date – date of Study Day 1) + 1

Pre-study day: study day= (date – date of Study Day 1)

Study Day 1:

It is defined as the first day that AMG 510 is administered to the subject.

Treatment-Emergent Adverse Event (TEAE):

An adverse event that occurs on or after the first administration of AMG 510 or within 30 days after the last dose of AMG 510. The severity of each adverse event will be graded using the CTCAE version 4.0. Adverse events will be coded using MedDRA 21.0.

Treatment-Related AE:

A treatment-related AE is any treatment-emergent AE that per investigator review has a reasonable possibility of being caused by the investigational product.

Toxicity Probability Interval (TPI):

Toxicity probability intervals for dose-limiting toxicity (DLT) are defined as (0.20, 0.33] and (0.33, 1.00] for target and excessive, respectively.

6. Analysis Sets

The following sub-sections describe the analysis sets to be used.

6.1 Full Analysis Set

Not applicable to this study.

6.1.1 Primary Analysis Set

Not applicable to this study.

6.2 Safety Analysis Set

Safety Analysis Set is defined as 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.

6.3 Per Protocol Set(s)

Not applicable to this study.

6.4 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

The PK Analysis Set will contain all subjects who have received at least 1 dose of the investigational product 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. The PK Analysis Set will be used to conduct the analysis of PK data, unless otherwise specified.

6.5 Interim Analyses Set(s)

Not applicable to this study. At interim analysis with cutoff determined, the DLT data will be analyzed based on DLT analysis set, PK parameters will be analyzed based on PK Analysis Set, and other data will be reported using Safety Analysis Set, unless otherwise specified.

6.6 DLT Evaluable Set

The Dose Limiting Toxicity Analysis Set will contain DLT-evaluable subjects. For dose-escalation decisions, backfill subjects will not be included (see protocol Section 5.1). The details of DLT evaluable subjects are given below:

Dose Cohort	Duration of DLT Window	DLT Evaluable Subject
Multiple subject cohorts	21 days from C1D1	Subject experienced a DLT or Subject does not experience a DLT and subject received at least 80% of the planned doses (ie, no more than 4 days without dosing) of investigational product within the first treatment cycle of 21 days.

C1D1 = Cycle 1 Day 1; DLT = Dose-Limiting Toxicity

7. Planned Analyses

The following data analyses are planned:

- An interim analysis for efficacy parameters will be conducted after dose escalation is completed.
- The primary analysis will occur when target enrollment is complete, and each subject has had the opportunity to receive up to 6 months of treatment or terminated the study early.
- The final analysis is planned after all dose-escalation cohorts and dose-expansion subjects have ended the study.

7.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. Based on accumulating toxicity information, BLRM will be used to make dosing recommendations based on the DLT Evaluable Set. In DLRMs, Amgen, in consultation with the site investigators, will review the BLRM recommended dose level and will review all available cumulative data by cohort prior to making dose escalation decisions. As a sensitivity analysis, a one-parameter Continual Reassessment Method (CRM) model may be used to estimate the dose-toxicity relationship to help make dose escalation decisions. Adverse events and DLTs observed in all subjects (including backfill subjects) will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions.

An interim analysis for efficacy parameters will be conducted after dose escalation is completed.

7.2 Primary Analysis

The primary analysis will occur when target enrollment is complete, and each subject has had the opportunity to receive up to 6 months of treatment or has terminated the study early.

7.3 Final Analysis

A final analysis is planned after all dose-escalation cohorts and dose-expansion subjects 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.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database. The database will be subject to edit checks outlined in the Clinical Data Management Plan (DMP). See details of this section in the DMP.

8.3 Handling of Missing and Incomplete Data

Incomplete adverse event and concomitant medication dates missing data will be imputed as described in Appendix A.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in each cohort. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

PK concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard PK evaluation practice.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required data transformations of analyses will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographic, safety and PD data. Unless otherwise stated, the data analysis will be conducted using subjects in the Safety

Analysis Set. Descriptive statistics on continuous data will include means, medians, standard deviations, minimums & maximums while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

9.2 Subject Accountability

The number and percent of subjects who were enrolled, received investigational product, discontinued from investigational product (including reasons for discontinuing, completed study, discontinued the study (including reasons for discontinuing) will be summarized. Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented.

A subject listing and summary noting inclusion in each analysis subset will be provided for all subjects enrolled. A subject listing noting AMG 510 administration start and end time, reason for discontinuation of treatment, and reason for discontinuing the study will be provided. A list of subjects screened but not enrolled (screen failures) may be provided.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the study. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations will be provided.

9.4 Demographic and Baseline Characteristics

The following descriptive summaries of the demographic and baseline characteristics will be produced: Demographic (ie, age, age groups [< 65, >= 65 and >= 75], sex, race, ethnicity) and baseline characteristics, which may include height, weight, BMI, Eastern Cooperative Oncology Group (ECOG) Performance Status, ECHO or MUGA, prior anti-cancer systemic therapy [1, 2, >2)) will be summarized using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple.

A listing of the demographic and baseline characteristics will be provided. In addition, listings of medical and surgical history, prior anti-cancer therapy, prior surgery and prior radiotherapy usage will be provided.

9.5 Efficacy Analyses

The efficacy endpoints include ORR, OS, DCR, DOR and PFS. In general, the analysis of efficacy endpoints will be based on the Safety Analysis Set unless otherwise specified. The efficacy endpoints will be analyzed overall, by dose (eg, MTD / RP2D), regimen (if more than one evaluated), and by histologic type, if appropriate.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

No efficacy parameter is considered in primary endpoints.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The number and percent of subjects with best overall response of complete response, partial response, stable disease, and progressive disease as determined will be tabulated.

The proportion of subjects with an objective response (CR or PR) and disease control (CR, PR or SD > 6 months) with corresponding exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) and tabulated for subjects treated at the MTD or RP2D.

A Kaplan-Meier (K-M) curve may be presented for duration of overall response, duration of stable disease, overall survival and progression-free survival with estimates for rates and 95% CI at selected months. K-M curve can be done for DOR, if at least 10 subjects have a CR/PR.

Descriptive statistics including means, standard deviations, medians, minimums, and maximums for duration of overall response and duration of stable disease.

Listings will be produced for all subjects in Safety Analysis Set indicating their best overall response, duration of overall response, overall survival, progression-free survival, and duration of stable disease.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

No efficacy parameter is considered in primary endpoints.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

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 at least 1 dose of AMG 510.

Subject incidence of DLTs will be used to fit the BLRM model to estimate the probability of having a DLT across dose levels.

9.6.2 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and death due to adverse events.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order.

The number and percentage of subjects reporting adverse events will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.

The severity of each adverse event will be graded using The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 criteria

- **http://ctep.cancer.gov/protocolDevelopment/electronicapplications/ctc.htm.**

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

A listing of the adverse events & serious adverse events will be provided.

9.6.3 Laboratory Test Results

Individual chemistry, hematology, urinalysis, coagulation urine/serum pregnancy test (females only and not required if surgically sterile or ≥ 2 years postmenopausal) laboratory data will be listed and selected parameters may be plotted. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings.

CTCAE grades will also be highlighted where appropriate. The number and percentage of subjects experiencing treatment emergent laboratory toxicities with worst post dose CTCAE grades of ≥ 1, ≥ 2, ≥ 3 and 4 will be presented. The direction of the laboratory worsening will be denoted. The summary will be presented for all laboratory parameters for which at least one subject experienced a treatment emergent toxicity with a worst grade ≥ 3. Additionally, the number and percentage of subjects experiencing 1, 2, 3 and 4 worsening CTCAE grade shifts from baseline will be presented. The direction of the

laboratory worsening will again be denoted. Unscheduled assessments will be incorporated in the laboratory analyses where possible.

Shifts tables indicating the change between the baseline and the maximum post dose CTCAE grades for an increased value and the maximum post dose grade for a decreased value will be provided for selected laboratory parameters of interest.

A listing of CTCAE grade 3 or higher laboratory toxicities will be provided. This listing will include all laboratory data for the subject and laboratory parameter of interest in order to provide proper context. A flag will indicate the grade 3 or higher toxicity.

Summaries of the absolute value and/or changes from baseline at each scheduled assessment may be provided for selected laboratory parameters.

A summary of the change from baseline to the post dose maximum, time to post-dose maximum, change from baseline to the post dose minimum, and the time to the post dose minimum may also be provided for selected parameters.

Potential Hy's law cases will be listed and may also be summarized.

9.6.4 Vital Signs

Vital signs data (eg, systolic / diastolic blood pressure, heart rate, respiratory rate, temperature and pulse oximetry) will be listed and reviewed for each subject. Summary statistics for each vital sign parameter will be provided for baseline and each scheduled post-baseline assessment. Depending on the size and scope of changes, summaries of changes from baseline over time may be provided. Unscheduled assessments will be included in this summary.

Shifts in scores for ECOG performance status scores between the baseline and each assessed time point will be tabulated. ECOG performance status scores will be summarized at relevant time points.

9.6.5 Physical Measurements

Physical measurement data will be listed and reviewed for each subject. Depending on the size and scope of changes, summaries of changes from baseline over time may be provided. Unscheduled assessments will be included in this summary

9.6.6 Electrocardiogram

A set of triplicate ECGs must be performed at screening; all ECGs will be triplicates with each tracing 30 seconds apart

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

Subjects' maximum change from baseline in QT interval corrected by Fridericia's formula 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 presented and select parameters of interest may be plotted.

In addition, the relationship between AMG 510 exposure and change from baseline in QTc will be explored graphically.

9.6.7 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment dose, combining data for each study part. Number of cycles started, number of doses of investigational product, the cumulative dose by unit and average dose delivered per day will be summarized. Summaries of the number and percentage of subjects with dose modifications and reason for modification will be provided.

Details for each AMG 510 administration will be listed for every subject. In addition, a listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

9.6.8 Exposure to Other Protocol-required Therapy

Not applicable for the study.

9.6.9 Exposure to Concomitant Medication

The number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category as coded by the World Health Organization Drug (WHO DRUG) dictionary.

A subject listing of all prior and concomitant medications will be presented.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Nominal sampling times will be used for individual concentration-time plots and tables. Actual dose administered, and actual sampling times will be used for the calculation of

PK parameters for each subject. The reasons for excluding any sample from the analyses will be provided.

Individual concentration-time data will be tabulated and presented graphically. Summary of PK concentration over time and PK parameters will be provided. Mean concentration-time profiles for each dose will be provided.

PK parameters will include, but are not limited to maximum observed concentration (C_{max}), time to maximum concentration (t_{max}) and area under the plasma concentration-time curve (AUC). Other PK parameters such as AUC from time 0 to the time extrapolated to infinity (AUC_{inf}), apparent clearance (CL/F), and terminal half-life ($t_{1/2}$) may be analyzed. Pharmacokinetic parameters will be estimated using standard non-compartmental approaches based on the PK Analysis Set and summarized by dose level using descriptive statistics including, but not limited to means, standard deviations, medians, minimums, and maximums. Above analyses will be conducted by Amgen Clinical Pharmacology Modeling and Simulation (CPMS).

For the food-effect assessment, PK parameter estimates will help assess the impact of food on the pharmacokinetics of AMG 510. The geometric means and 90% confidence interval for the ratio of the geometric means (fed state/fasted state) will be estimated using a mixed-effects model. The model will use the log-transformed PK parameters as the dependent variable (or response) and treatment conditions (fed versus fasted) as the independent variable.

The median of t_{max} will be compared between fasted and fed conditions.

9.7.2 Analyses of Clinical Outcome Assessments

Not applicable for this study.

9.7.3 Analyses of Health Economic Endpoints

Not applicable for this study.

9.7.4 Analyses of Biomarker Endpoints

Relationships between changes in tumor dynamics and above biomarkers of interest listed as exploratory endpoints will be explored. Changes in expression levels of biomarkers and their relationship to dose may also be explored. Summary statistics over time will be provided and graphical presentations may be used.

The relationship between AMG 510 exposure and related biomarkers in blood will be also explored if deemed appropriate. As appropriate, details of analysis will be provided in a supplemental analysis plan for exploratory biomarker analysis.

10. Changes From Protocol-specified Analyses

Overall Survival added for the secondary endpoint analyses.

11. Literature Citations / References

Babb J, Rogatko A, Zacks S. Cancer Phase I Clinical Trias: Efficient Dose Escalation with Overdose Control. Statistics in Medicine 1998; 17:1103-1120

Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clinical Trials. 5(2):93-106. 2008

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008 Jun 15; 27(13):2420-39.

Clopper C.J. and Pearson E.S. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika Vol. 26, No. 4 (Dec., 1934): 404-413

12. Prioritization of Analyses

No priority of output is planned for this study.

13. Data Not Covered by This Plan

The analysis of Biomarkers is not covered in this plan

14. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial.

		Stop Date						
		Complete: yyyymmdd		**Partial: yyyymm**		**Partial: yyyy**		
Start Date		**< 1st Dose**	**≥ 1st Dose**	**< 1st Dose yyyymm**	**≥ 1st Dose yyyymm**	**< 1st Dose yyyy**	**≥ 1st Dose yyyy**	**Missing**
Partial: yyyymm	**=1st Dose yyyymm**	2	1	2	1	N/A	1	1
	≠ 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	**=1st Dose yyyy**	3	1	3	1	N/A	1	1
	≠ 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

Imputation Rules for Partial or Missing Start Date:

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Appendix B. Code Fragments

Provisional Code Fragments for calculating a confidence interval using the Clopper Pearson Method. The following example SAS code will be utilized for the response rate analysis providing the proportion of subjects responding to treatment with corresponding 95% confidence intervals and 90% confidence intervals.

For 95% confidence intervals:

```
data propci (keep = ns p low_ci upp_ci);
n=xx; * total n within the treatment group;
ns= xx; *number of responders;
p=ns/n; * response rate;
q=1-p;
lowF=FINV(0.025, 2*ns, 2*(n-ns+1)); /* use for 2-sided 95% CI */
UppF=FINV(1-0.025, 2*(ns+1), 2*(n-ns)); /* use for 2-sided 95% CI */
low_ci = 1 / (1+(n-ns+1) / (ns*lowf)); * lower CI for response rate;
upp_ci = 1 / (1+(n-ns) / ((ns+1)*uppf)); *upper CI for response rate;
if p=1 then upp_ci=1;
if p=0 then low_ci =0;
output;
end;run;
```

For 90% confidence intervals.

```
data propci (keep = ns p low_ci upp_ci);
n=xx; * total n within the treatment group;
ns= xx; *number of responders;
p=ns/n; * response rate;
q=1-p;
lowF=FINV(0.05, 2*ns, 2*(n-ns+1)); /* use for 2-sided 90% CI */
UppF=FINV(1-0.05, 2*(ns+1), 2*(n-ns)); /* use for 2-sided 90% CI */
low_ci = 1 / (1+(n-ns+1) / (ns*lowf)); * lower CI for response rate;
upp_ci = 1 / (1+(n-ns) / ((ns+1)*uppf)); *upper CI for response rate;
if p=1 then upp_ci=1;
if p=0 then low_ci =0;
output;
```

A linear mixed effect model using Proc Mixed of SAS was used to analyze logarithmically transformed AUC and C_{max} in fasted vs. fed state. The geometric means

and 90% confidence interval for the ratio of the geometric means (fed state/fasted state) will be estimated using a mixed-effects model.

```
proc mixed data=<data_set_name> method=reml;
    class subject visit food_conditions;
    model response = food_conditions /outp=outp ddfm=kr residual;
    random usubjid / type=un;
    lsmeans food_conditions *visit/ ALPHA=0.1cl;
    ods output lsmeans=lsmeans diffs=diffs;
run;
conditions
Where,
response = log-transformed PK parameters
food_conditions = fed & fasted
Programming Note: In case if model doesn't converge change the covariance
structure from type=UN to the below order
1.  type = AR(1); if AR(1) doesn't converge then use
2.  type = CS
```

Statistical Analysis Plan

Protocol Title:	A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 Monotherapy in Subjects With Advanced Solid Tumors With *KRAS p.G12C* Mutation and AMG 510 Combination Therapy in Subjects With Advanced NSCLC With *KRAS p.G12C* Mutation
Short Protocol Title:	AMG 510 Phase 1/2
Protocol Number:	20170543
NCT Number:	NCT03600883
Authors:	[redacted]
Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320 Phone: +1 805-447-1000
SAP Date:	**Document Version** — **Date** **Amendment 1 (v2.0)** — 16 July 2019

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	14NOV2018	Original SAP
Amendment 1 (v2.0)	16JUL2019	Add phase 2 portion and analyses per Protocol Amendment 3 (22 May 2019)

Table of Contents

List of Tables

List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ANC	Absolute neutrophil count
AUC	Area under the concentration-time curve
ALK	Anaplastic lymphoma kinase
BID	Twice daily
BLRM	Bayesian Logistic Regression Model
Cmax	Maximum observed concentration
CR	Complete response
CRC	Colorectal cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DOR	Duration of response
DRT	Data Review Team
ECG	Electrocardiogram
EQ-5D-5L	EuroQol-5 Dimension
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30
FDA	Food and Drug Administration
FIH	First-in-human
ICF	Informed consent form
ICH	International Conference of Harmonization
IVD	In vitro diagnostic
IR	Immediate-release
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
KRASG12C	KRAS protein with a G12C mutation at the protein level
KRAS p.G12C	KRAS DNA with a mutation resulting in a G12C mutation at the protein level
MRI	Magnetic resonance imaging
NSCLC	Non-small-cell lung carcinoma
ORR	Objective response rate
OS	Overall survival

Abbreviation or Term	Definition/Explanation
PD	Progressive disease
PK	Pharmacokinetic(s)
PO	Oral(ly)
PFS	Progression-free survival
PR	Partial response
PRO	patient-reported outcomes
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
QD	Once daily
QLQ-LC13	Quality-of-Life Questionnaire Lung Cancer Module
QLQ-PAN26	Quality-of-Life Questionnaire Pancreatic Cancer Module
QOL	Quality of Life
QTc	Corrected QT (interval)
RAS	Rat sarcoma viral oncogene homolog
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 Dose
SD	Stable disease
tmax	Time to reach maximum concentration
TTR	Time to response

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within Amendment 3 of the protocol for study 20170543, AMG 510 dated 22 May 2019. The scope of this plan includes the interim analysis, the primary analysis and the final analysis in Phase 1 and the interim analysis, the primary analysis, additional analysis subsequent to the primary analysis, and the final analysis in Phase 2 that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

2.1.1 Phase 1 (Monotherapy - Parts 1a, 1b, and 2a)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of AMG 510 in adult subjects with *KRAS p.G12C* mutant advanced solid tumors • To estimate the maximum tolerated dose (MTD) and/or a recommended phase 2 dose (RP2D) in adult subjects with *KRAS p.G12C* mutant advanced solid tumors	• Subject incidence of treatment-emergent adverse events, treatment-related adverse events, and clinically significant changes in vital signs, physical examinations, electrocardiograms (ECGs), and clinical laboratory tests • Subject incidence of dose limiting toxicity (DLT)
Secondary	
• To characterize the pharmacokinetics (PK) of AMG 510 following administration as an oral tablet formulation	• PK parameters of AMG 510 including, but not limited to, maximum plasma concentration (C_{max}), time to achieve Cmax (t_{max}), and area under the plasma concentration-time curve (AUC)
• To evaluate tumor response assessed by response evaluation criteria in advanced solid tumors (RECIST) 1.1 of AMG 510 as monotherapy in advanced solid tumors with *KRAS p.G12C* mutation	• ORR, DOR, DCR, PFS, duration of stable disease, and TTR measured by CT or MRI and assessed per RECIST 1.1. Response will be assessed by independent radiologic review. Complete response and PR require confirmatory CT or MRI repeat assessment 4 weeks after the first detection of response.
• To evaluate the effect of food on the oral PK of AMG 510	• PK parameters of AMG 510 including, but not limited to, C_{max}, t_{max}, and AUC in the fed and fasted states for the food effect assessment
• To evaluate the relationship between changes in corrected QT interval (QTc) and AMG 510 exposure	• AMG 510 exposure/QTc interval relationship

Objectives	Endpoints
Exploratory	
• To explore pharmacodynamic relationships for safety and/or efficacy endpoints	• AMG 510 exposure/safety and exposure/efficacy relationships • Pharmacodynamic changes observed in blood and/or biopsies if available
• To characterize AMG 510 excretion in urine	• AMG 510 excretion in urine
• To identify metabolites of AMG 510 in plasma and urine	• Characterization of potential metabolites of AMG 510 in plasma and urine, if appropriate
• To investigate potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor tissue samples.	• Quantification of biomarker expression at protein, RNA, and DNA levels, as appropriate • Potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor tissue samples

[redacted]

2.1.3 Phase 2 (AMG 510 Monotherapy)

Objectives	Endpoints
Primary	
• To evaluate tumor objective response rate (ORR), assessed by RECIST 1.1 criteria, of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors (NSCLC, colorectal cancer [CRC], and other tumor types).	• Objective response rate (ORR = complete response [CR] + partial response [PR]), assessed per RECIST 1.1. Response will be assessed by independent radiologic review. Complete response and PR require confirmatory CT or MRI repeat assessment 4 weeks after the first detection of response.
Secondary	
– To evaluate other measures of AMG 510 efficacy as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors by RECIST 1.1 (NSCLC, CRC, and other tumor types). • Duration of response (DOR) • Disease control rate (DCR) • Time to response (TTR) • Progression-free survival (PFS) • Overall survival (OS) • PFS rate at 6 months and 12 months • OS rate at 12 months	• Duration of response - defined as time from first evidence of confirmed PR or CR to disease progression or death due to any cause, whichever occurs first. Subjects without a duration ending event will be censored at their last evaluable disease assessment date. Progression will be based on an independent radiologic assessment of disease response per RECIST 1.1 • Disease control rate defined as CR + PR + stable disease rate measured as described for ORR • Time to response - defined as time from first dose of AMG 510 until the first evidence of confirmed PR or CR • Progression-free survival - defined as time from first dose of AMG 510 until disease progression or death from any cause, whichever occurs first. Subjects who do not progress or die will be censored at their last evaluable disease assessment date. Progression will be on an independent radiologic assessment of disease response per RECIST 1.1. • Overall survival - defined as time from first dose of AMG 510 until death from any cause. Subjects who do not die will be censored at the date of last contact. • Progression-free survival rate at 6 months and 12 months • Overall survival rate at 12 months
• To evaluate the safety and tolerability of AMG 510 in adult subjects with *KRAS p.G12C* mutant advanced solid tumors (NSCLC, CRC, and other tumor types).	• Subject incidence and severity of adverse events
• To evaluate the PK of AMG 510 following administration as an oral tablet formulation	• Pharmacokinetics parameters of AMG 510 including, but not limited to, C_{max}, t_{max}, and AUC.

Objectives	Endpoints
Exploratory	
• To explore PK/pharmacodynamic relationships for safety and/or efficacy endpoints	• AMG 510 exposure/safety and exposure/efficacy relationships • Pharmacodynamic changes observed in blood and/or biopsies if available
• To explore biomarkers of response and resistance in tumor and blood specimens prior to exposure to AMG 510 and at the time of progression	• Biomarkers of response and resistance to AMG 510 at the time of progression – Quantification of biomarker expression at protein, RNA, and DNA levels, as appropriate – Potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor tissue samples
• To explore the subject experience with AMG 510 treatment using patient-reported outcome instruments with respect to the following core concepts: – Impact of treatment on disease-related symptoms and Health-related Quality of Life (HRQOL) – Treatment-related symptoms and impact on the subject – Physical function	• Changes in cancer-specific symptoms and overall health status using subject-reported outcome instruments: – Impact of treatment on disease-related symptoms and HRQOL (instruments; EORTC QLQ-C30 + disease-specific modules QLQ LC13 and NSCLC SAQ for NSCLC, and QLQ Pan 26 for pancreatic cancer) – Treatment-related symptoms and impact on the subject (EORTC QLQ-C30, selected questions from the PRO-CTCAE library and a single item about symptom bother, item GP5 of the FACT-G) – Physical function (instrument: EORTC QLQ-C30, Physical function scale)

2.2 Hypotheses and/or Estimations

Phase 1 (monotherapy [redacted]

- At least 1 dose level of AMG 510, in repeat oral administrations, will achieve acceptable safety and tolerability in subjects with *KRAS p.G12C* mutant advanced solid tumors in both monotherapy [redacted]
- A favorable PK profile will be achieved with AMG 510 administered orally as monotherapy [redacted]
- Responses will be observed at a monotherapy dose level that achieves acceptable safety and tolerability.

Phase 2 (AMG 510 monotherapy):

A clinically relevant ORR will be observed in each tumor type (NSCLC, CRC or other tumor type) at a dose level that demonstrates acceptable safety and tolerability

3. Study Overview

3.1 Study Design

This is a phase 1/2 multicenter, non-randomized, open-label study of orally administered AMG 510 in subjects with *KRAS p.G12C* mutant advanced solid tumors. The study will be conducted at approximately 100 sites globally.

Phase 1 is a first in human (FIH) dose exploration/expansion study to define the MTD or RP2D, safety, tolerability, PK and pharmacodynamics of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors (Phase 1, Part 1a, 1b, and 2a) [redacted] The phase 1 portion of the study will be conducted in 2 parts: part 1 – Dose Exploration and part 2 – Dose Expansion. Part 1 is aimed at evaluating the safety, tolerability, PK, and pharmacodynamics and determining the MTD of repeat daily (QD) (or twice daily [BID]) dosing for AMG 510 monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors using a Bayesian Logistics Regression Model (BLRM) design and evaluating the safety, tolerability, [redacted] The dose expansion part of the study (part 2) can open once the MTD and/or a RP2D has been determined in part 1. The DLT evaluation period will be 21 days.

Phase 2 is a multicenter, non-randomized, open-label, phase 2 study to evaluate efficacy and safety/tolerability of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors (NSCLC, CRC, and other tumors).

Administration of AMG 510 may continue until subject has confirmed disease progression or discontinues from the treatment for reasons listed in Protocol Section 8.3.1.

Phase 1:

Dose Exploration – Part 1

Part 1a Monotherapy Cohorts (Once Daily Dosing – QD):

Dose exploration monotherapy cohorts will estimate the MTD, and evaluate the safety, tolerability, PK, and pharmacodynamics of different doses of AMG 510 administered orally once daily in subjects with *KRAS p.G12C* mutant advanced solid tumors. Enrollment into the dose exploration cohorts may be from any eligible solid tumor type. Dose escalation will begin with 2-4 subjects treated at the lowest planned dose level of

180 mg. Dose escalation will follow the planned schedule with 2-4 subjects treated in each cohort. If no DLT is observed, dose escalation will continue to the next planned dose cohort as per Protocol Table 1. In addition to the dose levels outlined in Protocol Table 1, intermediate doses of 270 mg and 540 mg may be explored. Upon escalation to the next planned dose cohort, sentinel dosing will apply. There will be a 2-day window between the first subject dosed and subsequent subjects. Once a subject experience a DLT, dosing for subsequent cohorts will be recommended using the dose level recommendation from the BLRM. The decision to advance to the next dose level will be recommended by the Dose Level Review Team (DLRT) using the dose level recommendation from BLRM, as appropriate, and by evaluating available safety data, laboratory, and PK information.

Intra-subject dose escalations are allowed on this study. Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle if the next dose cohort is deemed safe at that time by the DLRT and after consultation with the sponsor if:

- no DLT has been reported for this subject during or after completion of the DLT period
- the subject has not experienced any $\geq$ grade 2 adverse events (deemed treatment related by the investigator) during treatment

Subjects who proceed to a higher dose level will be required to have back to back clinic visits on day 1 and day 2 at the beginning of the cycle with the higher dose. The safety assessments of chemistry and urinalysis will be performed on day 1 and day 2. A repeat of PK sample collection will be performed as on cycle 1 day 1 and cycle 1 day 2, regardless of actual study cycle.

Subjects who do not proceed to a higher dose may continue to receive additional cycles at the original dose.

Dose exploration will continue until any of the following events.

- the highest planned dose level is determined to be safe and tolerable (minimum of 6 DLT-evaluable subjects)
- the MTD is identified, BLRM recommends a dose level which already has 6 DLT-evaluable subjects

Additional subjects (20 to 40) may be enrolled in one or more monotherapy dose levels that have been shown to be safe and tolerable; defined as backfill enrollment. This backfill enrollment will be done to better estimate the RP2D and better characterize the

safety, efficacy, PK, and pharmacodynamics for AMG 510 monotherapy and may be concurrent with dose escalation to identify the MTD. Additionally, food effect assessment will be conducted in at least 6 subjects from backfill enrollment in cycle 2 or later.

Part 1b Monotherapy Cohorts (Twice Daily Dosing – BID):

A BID dosing schedule for AMG 510 may be investigated as a dose modification strategy to potentially optimize AMG 510 activity. The initiation of the BID dosing schedule will be based upon the totality of the data available from Part 1a and food effect assessment. Approximately 12 subjects may be enrolled in 2 cohorts of 3 to 6 subjects per cohort.

[redacted]

Dose Expansion – Part 2

Upon completing the dose exploration part of the study and depending on data obtained, dose expansion may proceed with 2 groups consisting of subjects with *KRAS p.G12C* mutant solid tumors:

- Part 2a subjects with *KRAS p.G12C* mutant advanced NSCLC, CRC, or other tumor types administered AMG 510 monotherapy once daily (total approximately n = 20, maximum n = 60).
- [redacted]

Dose expansion in these 2 groups may be done concurrently.

Transition from Monotherapy Phase 1 (Part 2a) Dose Expansion to Phase 2:

After a minimum of 20 subjects have been enrolled to the initial estimated monotherapy RP2D (including subjects enrolled to the RP2D in either the dose exploration or the dose expansion parts of the study) and have completed the 21-day DLT period, the DLRT will review all available safety, laboratory, PK, and efficacy (physician assessment) data (including all previous data from the dose expansion and backfill cohorts). Antitumor activity will also be monitored in terms of ORR by tumor types (NSCLC, CRC). Futility and efficacy thresholds will be calculated using Bayesian posterior probability approach based on the cumulative efficacy data and it will serve as a guidance to the DLRT. DLRT will make a recommendation as to whether to proceed to the phase 2 monotherapy part of the study. The DLRT may also recommend that additional subjects be enrolled at this estimated monotherapy RP2D or that a dose reduction or alternate dosing regimen be explored before proceeding to phase 2. After this first review has been conducted, if a decision is made to continue to obtain additional data at the initial estimated RP2D prior to proceeding to phase 2, the intervals for subsequent reviews will be determined by the DLRT but should occur within a maximum of 20 additional subjects enrolled and dosed for 21 days. The maximum number of subjects that may be enrolled to the initial estimated RP2D in the monotherapy dose expansion group, without confirmation of this dose for phase 2, will not exceed 60. If another dose (or schedule) needs to be explored, additional subjects on that dose (or schedule), up to a total of 60, may be enrolled. Whenever DLRT will review the data, the futility and efficacy thresholds will be calculated based on all the cumulative efficacy data to provide the guidance.

Phase 2:

This is a multicenter, non-randomized, open-label, phase 2 study to evaluate efficacy and safety/tolerability of AMG 510 as monotherapy in subjects with *KRAS p.G12C* mutant advanced solid tumors (NSCLC, CRC, and other tumors). The dose (and schedule) administered in phase 2 will be that confirmed to be the RP2D from combined analyses of phase 1 part 1 and 2. Approximately 200 subjects (at least 105 for NSCLC and 60 CRC) will be enrolled. The timing to start enrollment into each tumor type will be communicated to the sites and may be gated based on Amgen's internal decision based on several factors (ie, efficacy and availability of the drug supply). Tumor response will be evaluated employing RECIST 1.1 based on contrast enhanced computed tomography (CT)/magnetic resonance imaging (MRI) with assessments conducted by an independent radiological central laboratory. Interim safety reviews will be conducted after 30, 50, 70, and 100 subjects have been enrolled and treated with AMG 510 for at least 21 days (enrollment will not be held for completion of these safety reviews). Interim futility analyses will be conducted as described in Section 7.1 Interim Analysis and Early Stopping Guideline.. The primary analysis for phase 2 will occur when 105 NSCLC subjects or 60 CRC subjects are enrolled and have 6-month follow-ups (Section 7.2 Primary Analysis), whichever group occurs first. The data cutoff was decided to allow sufficient time to demonstrate durability of ORR.

3.2 Sample Size

It is anticipated that up to 158 subjects will be enrolled in the phase 1 part of the study. No more than 92 subjects will be enrolled in part 1 (dose exploration) cohorts and up to 66 subjects will be enrolled in part 2 (dose expansion) cohorts.

Part 1 – Dose Exploration:

Part 1a

Approximately 30 subjects will be needed to estimate the AMG 510 monotherapy MTD in part 1a. An additional 20 to 40 subjects may be enrolled by backfill enrollment and receive AMG 510 monotherapy (part 1a) from which at least 6 subjects will be evaluated for food effect.

Part 1b

Approximately 12 subjects may be enrolled in 2 cohorts of 3 to 6 subjects per cohort.

[redacted]

Part 2 – Dose Expansion: Approximately 20 subjects (maximum of 60 subjects) with *KRAS p.G12C* mutant advanced tumors (of any tumor type) will be enrolled at the initial estimated RP2D in the part 2a monotherapy dose expansion part of the study.

[redacted]

Phase 2:

In phase 2, it is anticipated that approximately 200 subjects (at least 105 subjects with NSCLC and 60 subjects with CRC) will be enrolled. Actual enrollment for each tumor type (NSCLC, CRC) will be based on DLRT recommendations and Amgen's internal decision.

The rationale for the number of subjects is provided in protocol Section 10.2.

3.3 Adaptive Design

For Phase 1 dose exploration, the adaptive features of the BLRM design are described in Protocol Appendix E. For Phase 1 dose expansion, the futility and efficacy thresholds are calculated and specified in Section 7.1.2. For Phase 2, futility analyses are described in Section 7.1.3.2.

4. Covariates and Subgroups

4.1 Planned Covariates

The following baseline covariates may be used to evaluate efficacy endpoints in subgroups or in multivariate analysis: Age at baseline (< 65, >= 65 years), prior lines of anti-cancer therapy (1, 2, >2) and ECOG performance status.

4.2 Subgroups

In Phase 2, the following subgroup may be used to examine the primary and selected secondary endpoints, as appropriate. When there is not a sufficient number of subjects in the subgroup (ie, less than 10% of the whole population), relevant subgroups may be combined.

- Age at baseline (<65, >=65 years)
- Prior lines of anti-cancer therapy (1, 2, >2)
- Prior immunotherapy treatment

- ECOG (0, 1)
- Race (Caucasian, black, other)
- Sex (male, female)
- Histology (adenocarcinoma or squamous cell carcinoma)
- Stages (locally advanced and unresectable vs metastatic)
- Presence of liver metastasis (yes, no)
- Presence of brain metastasis (yes, no)
- Co-mutation of interest
- Smoking history
- Region (North America and Europe vs rest of world)
- Best response on prior therapy

Biomarker data may be incorporated in additional exploratory subgroup or multivariate analyses. The analyses of biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoints.

5. Definitions

Adverse Event (AE):

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.

The definition of adverse events includes worsening of a preexisting medical condition. A preexisting condition that has not worsened during the study, or involves an intervention, is not considered an adverse event.

Age at Enrollment:

Subject age at enrollment will be determined using the age in years reported in the clinical database.

AUC:

The area under the plasma drug concentration-time curve (AUC) reflects the actual body exposure to drug after administration of a dose of the drug.

Baseline:

For any variable, unless otherwise specified the baseline is the last non-missing assessment taken prior to the first administration of any study specified treatment. Where baseline measurements are taken on the same day as the study specified

treatment and no times are present, it will be assumed that these measurements are taken prior to the study specified treatment being administered.

Baseline ECG Values in Triplicate:

The mean of the three triplicate ECG results should be calculated for Baseline. If fewer than three triplicate ECG results are available, the mean of available triplicate should be calculated. For all post-baseline ECG, the mean of one triplicate ECG results at the same assessment will be calculated and used in the analysis.

When an ECG is missing within a triplicate, all available data will be averaged for that time point.

Best Overall Response (BOR):

Best overall response (BOR) for a subject is the best observed disease response per RECIST v1.1. Overall response assessments occurring after the start of the first subsequent anticancer therapy will not be included. No additional derivations will be required to classify the response.

BOR is defined as the best response in the following order: CR, PR, SD, PD, or NE, where CR and PR require confirmation by a repeat, consecutive scan at least 4 weeks after the first documentation of response. A best overall response of SD requires an on-study imaging of SD or better no earlier than 6 weeks after cycle 1 day 1; otherwise the best overall response will be not evaluable (NE)

Please refer Protocol Appendix D for more details.

Body Mass Index (BMI):

Body Mass Index should be calculated using the following formula:

$BMI\ (kg/m^2) = weight\ (kg) / [height\ (cm)/100]^2$

Body Surface Area (BSA):

The Body Surface Area should be calculated using the following formula:

$BSA = 0.007184 \times weight(kg)^{0.425} \times height(cm)^{0.725}$

Change from Baseline:

Change from Baseline is the arithmetic difference between post-dose assessments and Baseline value.

Change (absolute) from Baseline = (Post-baseline Value – Baseline Value)

Change (percent) from Baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

Dose Limiting Toxicity (DLT):

Dose-limiting toxicity (DLT) is defined as AMG 510-related toxicity with an onset within the first 21 days following first dose with the criteria defined in section 6.1.1.2.1 of the Protocol.

Disease control rate (DCR):

DCR is defined as the proportion of patients in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD) > 6 weeks.

Duration of response (DOR):

The duration of response is defined as time from first evidence of PR or CR to disease progression or death due to any cause.

The duration of complete response is defined as time from the first evidence of CR to disease progression or death due to any cause.

DOR will be calculated only for subjects who achieve a confirmed best overall response of PR or better.

Subjects will be censored following the censoring strategy described in the definition of PFS time in Table 1.

Duration of stable disease:

Duration of stable disease will be measured from the start of treatment to disease progression or death due to any cause.

Subjects will be censored following the censoring strategy described in the definition of the PFS time in Table 1.

End of IP administration (End of IP Admin):

End of IP Admin for each subject is defined as the date the decision was made to end IP as recorded on the End of Investigational Product Administration CRF page.

End of Study (Individual Subject):

End of study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study CRF page.

End of Study (Primary Completion):

It is defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s), whether the study was conducted as planned in the protocol or was terminated early.

End of Study (End of Trial):

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 (eg, long-term follow-up), as applicable.

Fridericia-corrected QT Interval (QTcF):

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows:

$$QTcF=QT/(RR/1000)^{1/3}$$

Investigational Product:

The term 'investigational product' is used in reference to AMG 510.

[redacted]

Last Investigational Product Dose Date:

The last IP date for each subject is defined as the latest date IP administered.

Long Term Follow-Up:

Following the SFU visit, there will be a LTFU period during which data will be collected on the subjects' health condition, disease status, survival and subsequent anticancer treatment.

Also, for subjects who discontinued study treatment without confirmed disease progression or start of subsequent anticancer treatment, tumor assessments will continue during LTFU every 12 weeks (± 2 weeks) for up to 3 years after last subject enrolled or until confirmed disease progression, start of subsequent anticancer treatment, death, withdrawal of consent, loss to follow-up, or end of study.

Subjects who had confirmed disease progression or started subsequent anticancer treatment, will be followed via telephone every 12 weeks (± 2 weeks) for assessment of survival and documentation of anticancer treatment. Subjects will be followed for up to 3 years after last subject enrolled or until withdrawal of consent, loss to follow-up, or subject death, whichever occurs first.

Maximum Tolerated Dose (MTD):

A final estimate of the MTD will be made based on a Bayesian Logistic Regression Model (BLRM) utilizing all DLT-evaluable subjects from the dose exploration and dose expansion cohorts. Based on the BLRM, the MTD is defined as the dose with the highest probability of a DLT rate between the targeted toxicity (0.2, 0.33) interval while controlling the probability of excessive and unacceptable toxicity below 25%. The MTD will estimated separately by dosing regimen if multiple regimens are evaluated.

Objective Response Rate (ORR):

Objective response rate is defined as the proportion of patients with a BOR of CR or PR.

Overall survival (OS):

Overall survival (OS) is defined as the time from the start of treatment until event of death due to any cause. Subjects still alive will be censored at the date last known to be alive. If the date last known to be alive is after the date that triggers the analysis (ie, the data cutoff date), the subject will be censored at the analysis trigger date.

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) of Phase 2, for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

Progression Free-Survival (PFS):

The PFS is defined as interval from the start of treatment to disease progression or death due to any cause (whichever comes first). The censoring rules for the progression-free survival analysis are detailed in Table 1.

Table 1. Main PFS Definition

Situation	Date of Event or Censor	Outcome
No evaluable post-baseline tumor assessments, no death by data cutoff	Date of first dose	Censor
No surgical resection, no new anti-cancer therapy, did not withdraw consent to participate in the study and :		
Progression documented per RECIST v1.1 before any death by data cutoff	Date of first observation date of disease progression	Event
No progression, but death recorded by data cutoff	Date of death	Event
No progression nor death by data cutoff	Date of last evaluable assessment	Censor
Surgical resection/new anti –cancer therapy started or withdraw consent to participate in the study and:		
Progression documented per RECIST v1.1 before surgical resection/new anti-cancer therapy started or withdraw consent to participate in the study by data cutoff	Date of first observation date of disease progression	Event
Progression documented per RECIST v1.1 after surgical resection/new anti-cancer therapy started or withdraw consent to participate in the study and alive by data cutoff	Date of last evaluable scan before start of new ant-cancer therapy/surgical resection	Censor
Subject died subsequently on or prior to data cutoff	Date of death	Event
No progression nor death by data cutoff	Date of last evaluable scan before start of new anti-cancer therapy/surgical resection	Censor

Relative Dose Intensity:

Relative dose intensity is calculated as actual dose intensity / planned dose intensity, where

- Cumulative actual dose [mg] is defined as the total dose given during the study treatment exposure. For subjects who did not take any drug the cumulative actual dose by definition is 0 mg.
- Actual dose intensity for subjects with non-zero duration of exposure is defined as: cumulative actual dose [mg] / duration of exposure [days] where duration of exposure = date of last dose – date of first dose + 1. For subjects who did not take any drug the actual dose intensity is 0 mg/day.
- Cumulative planned dose is the per-protocol planned dose accumulated over the actual duration on study treatment.
- Planned dose intensity for subjects with non-zero duration of exposure is defined as: cumulative planned dose [mg] / duration of exposure [days] where duration of exposure = date of last dose – date of first dose + 1.

Safety Follow-Up:

It is defined as the subject visit up to 30 (+7) days after last dose of AMG 510 is received.

Study Day:

Post-study day: study day= (date – date of Study Day 1) + 1

Pre-study day: study day= (date – date of Study Day 1)

Study Day 1:

It is defined as the first day of the treatment being administered to the subject.

Time to Response (TTR):

Time to response is defined as time from the start of treatment until the first evidence of confirmed PR or CR.TTR will be calculated only for subjects who achieve a best overall response of PR or better

Treatment-Emergent Adverse Event (TEAE):

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Events CRF and up to and including 30 days after the last dose of investigational product or the End of Study date, whichever is earlier.

Treatment-Related AE:

A treatment-related AE is any treatment-emergent AE that per investigator review has a reasonable possibility of being caused by the investigational product.

Toxicity Probability Interval (TPI):

Toxicity probability intervals for dose-limiting toxicity (DLT) are defined as (0.20, 0.33] and (0.33, 1.00] for target and excessive, respectively.

6. Analysis Sets

6.1 Full Analysis Set

6.1.1 Phase 1 Full Analysis Set

The Phase 1 Full Analysis Set (P1FAS) is defined as all subjects that are enrolled in phase 1 and receive at least 1 dose of AMG 510. All safety and efficacy analysis for Phase 1 except the DLT analysis and interim ORR analysis will be performed on the P1FAS.

6.1.2 Phase 2 Full Analysis Set

The phase 2 full analysis set (P2FAS) will consist of all subjects that are enrolled in phase 2 and receive at least 1 dose of AMG 510. The analysis of safety, PFS, and OS for Phase 2 will be performed on the P2FAS.

6.2 Safety Analysis Set

The integrated Safety Analysis Set is defined as all subjects that are enrolled in phase 1 and phase 2 and receive at least 1 dose of AMG 510.

6.3 Per Protocol Set(s)

Not applicable to this study

6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

The analysis set for Health-related Quality of Life outcomes will be defined in a Supplemental Statistical Analysis Plan along with the planned analyses for these endpoints.

6.5 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

The PK Analysis Set will contain all subjects who have received at least 1 dose of the investigational product 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. The PK Analysis Set will be used to conduct the analysis of PK data, unless otherwise specified.

6.6 Interim Analyses Set(s)

Interim analyses for specific endpoints will use P1FAS, P2FAS, or those defined in Section 6.7.

6.7 Study-specific Analysis Sets

6.7.1 DLT Evaluable Set

The Dose Limiting Toxicity Analysis Set will contain DLT-evaluable subjects. The details of DLT evaluable subjects are given below:

Dose Cohort	Duration of DLT Window	DLT Evaluable Subject
Multiple subject cohorts	21 days from C1D1	Subject experienced a DLT or Subject does not experience a DLT and subject received at least 80% of the planned doses (ie, no more than 4 days without dosing) of investigational product within the first treatment cycle of 21 days.

C1D1 = Cycle 1 Day 1; DLT = Dose-Limiting Toxicity

6.7.2 Phase 1 Monotherapy RP2D ORR Analysis Set

The phase 1 monotherapy RP2D ORR analysis set (P1OAS) will consist of all subjects with confirmed KRASp.G12C status whose initial dose of AMG 510 is at the RP2D and received at least 1 dose of AMG 510 in the phase 1 monotherapy dose exploration part, or the phase 1 monotherapy dose expansion part, and had at least 6-week response data. Subjects who stopped disease assessments prior to 6 weeks will be included in this analysis set if the data cutoff is at least 6 weeks after their first dose date. The futility and efficacy thresholds will be calculated for monitoring the antitumor activity of monotherapy of AMG 510 during phase 1 expansion part using this analysis dataset.

6.7.3 Phase 2 ORR Analysis Set

The phase 2 ORR analysis set (P2OAS) will consist of all subjects in the phase 2 full analysis set who have had at least 6 weeks response data starting from day 1. Subjects who stopped disease assessments prior to 6 weeks will be included in this analysis set if the data cutoff is at least 6 weeks after their first dose date. The interim futility analysis, primary analysis, and final analysis of ORR, DOR, and TTR will be performed on the P2OAS.

7. Planned Analyses

The following interim, primary, and final analyses for phase 1 and phase 2 portions of the study are planned.

7.1 Interim Analysis and Early Stopping Guidelines

7.1.1 Phase 1 (Part 1 - Dose Exploration)

Safety data will be reviewed on an ongoing basis by Amgen. Based on accumulating toxicity information, BLRM will be used to make dosing recommendations based on the DLT Evaluable Set. In DLRMs, Amgen, in consultation with DLRT, will review the BLRM recommended dose level and will review all available cumulative data by cohort prior to making dose escalation decisions. As a sensitivity analysis, a one-parameter Continual Reassessment Method (CRM) model may be used to estimate the dose-toxicity relationship to help make dose escalation decisions. Adverse events and DLTs observed in all subjects (including backfill subjects) will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions.

The DLRT members, quorum, voting members, and recommendations are described in Protocol Section 10.4.1.1.

7.1.2 Phase 1 (Part 2 – Dose Expansion)

This same DLRT will be responsible for reviewing data in the dose expansion phase to confirm the RP2D and determine the benefit/risk of proceeding to the phase 2 part of the study. The dose expansion part of the study (phase 1 - part 2) can open once an MTD or a RP2D and dosing schedule has been estimated in the dose exploration part of the study (phase 1 – part 1). If no DLT is observed in phase 1 – part 1, the RP2D will be estimated based on composite review of PK, overall safety/tolerability, and observed responses. Further confirmation of the RP2D dose will be sought in the phase 1 part 2 dose expansion.

In the dose expansion, additional subjects will be enrolled at the RP2D estimated in the phase 1 part 1 dose exploration. After a minimum of 20 subjects have been enrolled to the initial estimated monotherapy RP2D (including subjects enrolled to the RP2D in either the dose exploration [approximately 6] or the dose expansion [approximately 14] parts of the study) and have completed the 21-day DLT period, and after a minimum of 10 of these subjects have at least 6 weeks of response data (including all previous data from the dose expansion and backfill cohorts), the DLRT will review all available safety, laboratory, PK, and efficacy (physician assessment) data.

After the first review has been conducted, if a decision is made to continue to obtain additional data at the initial estimated RP2D prior to proceeding to phase 2, the intervals for subsequent reviews will be determined by the DLRT but should occur within a maximum of 20 additional subjects enrolled and dosed for 21 days. The maximum number of subjects that may be enrolled to the initial estimated RP2D in the monotherapy dose expansion group, without confirmation of this dose for phase 2, will not exceed 60. If another dose (or schedule) needs to be explored, additional subjects on that dose (or schedule), up to a total of 60, may be enrolled.

Based on emerging clinical efficacy data, the number of subjects with specific tumor types may be restricted/specified in the expansion part.

Antitumor activity will be monitored in terms of ORR by tumor types (NSCLC, CRC). Futility and efficacy thresholds will be calculated using Bayesian posterior probability approach based on the cumulative efficacy data and it will serve as a guidance to the DLRT. Enrollment will not be held to conduct this assessment.

Whenever DLRT will review the data, and there are at least 5 evaluable subjects in the tumor type, the futility and efficacy thresholds for that tumor type will be calculated using

all the cumulative efficacy data in phase 1 Monotherapy RP2D ORR Analysis Set to provide the guidance. In the calculation of thresholds, a response is defined as either a confirmed or unconfirmed CR or PR as per RECIST 1.1.

7.1.2.1 Futility Thresholds

For NSCLC, the futility thresholds are calculated such that the Bayesian posterior probability of a true ORR ≤ 0.15 is > a high probability of 75%. For CRC, the futility thresholds are calculated such that the Bayesian posterior probability of a true ORR ≤ 0.05 is > than a high probability of 75%. A noninformative prior distribution of beta (1, 1) will be used.

NSCLC: probability (ORR ≤ 0.15) > 75%

CRC: probability (ORR ≤ 0.05) > 75%

7.1.2.2 Efficacy Thresholds

For NSCLC, the efficacy thresholds are calculated such that the Bayesian posterior probability of a true ORR > 0.25 is ≥ to a high probability of 60%. For CRC, the efficacy thresholds are calculated such that the Bayesian posterior probability of a true ORR > 0.1 is ≥ to a high probability of 60%. A noninformative prior distribution of beta (1, 1) will be used.

NSCLC: probability [ORR > 0.25] ≥ 60%

CRC: probability [ORR > 0.1] ≥ 60%

Table 2 and Table 3 are look up tables calculated for NSCLC and CRC, providing the detailed futility and efficacy thresholds with different numbers of response-evaluable subjects (having at least 6-week response data) when DLRT review the data. For example, at the time when DLRT plan to review the data, there are a total of 25 response-evaluable NSCLC subjects. If observing number of the response is ≤ 2, based on the table, the guidance will recommend not to continue due to the lack of efficacy. If observing number of the response is ≥ 7, the guidance will recommend continuing to phase 2. If the observing number of the response is in between and the total number of response-evaluable subjects at that RP2D has not reached the maximum 60, the guidance will recommend enrolling more patients in the phase 1 expansion cohort.

The operating characteristics of these thresholds are demonstrated assuming a minimal of 5 response-evaluable subjects per tumor type for the first DLRT review and

every 5 response-evaluable subjects thereafter. The actual sample size per tumor type at each look will depend on tumor type distribution. Table 4 and Table 5 show the cumulative probabilities of recommending DLRT to stop the trial due to lack of efficacy and the cumulative probabilities of recommending DLRT to continue to phase 2 given the true ORR ranging from 0.1 to 0.5 for NSCLC subjects and 0.05 to 0.25 for CRC subjects.

Table 2. Look Up Table for NSCLC Subjects

Number of Subjects	Recommend Not to Continue if Observing the Number of Responses Below
5 ~ 7	Never stop for futility with this number of subjects
8 ~ 16	0
17 ~ 24	≤ 1
25 ~ 31	≤ 2
32 ~ 39	≤ 3
40 ~ 47	≤ 4
48 ~ 54	≤ 5
55 ~ 60	≤ 6
Number of Subjects	Recommend Go to Phase 2 if Observing the Number of Responses below
5 ~ 8	≥ 2
9 ~ 11	≥ 3
12 ~ 15	≥ 4
16 ~ 19	≥ 5
20 ~ 23	≥ 6
24 ~ 26	≥ 7
27 ~ 30	≥ 8
31 ~ 34	≥ 9
35 ~ 38	≥ 10
39 ~ 42	≥ 11
43 ~ 46	≥ 12
47 ~ 50	≥ 13
51 ~ 54	≥ 14
55 ~ 57	≥ 15
58 ~ 60	≥ 16

NSCLC = non-small cell lung carcinoma

Table 3. Look Up Table for CRC Subjects

Number of Subjects	Recommend Not to Continue if Observing the Number of Responses Below
5 ~ 26	Never stop for futility with this number of subjects
27 ~ 52	0
53 ~ 60	≤ 1
Number of Subjects	Recommend Go to Phase 2 if Observing the Number of Responses Below
5 ~ 12	≥ 1
13 ~ 21	≥ 2
22 ~ 31	≥ 3
32 ~ 40	≥ 4
41 ~ 49	≥ 5
50 ~ 59	≥ 6
60	≥ 7

CRC = colorectal cancer

Table 4. Cumulative Probability of Go/No Go for NSCLC Subjects

Number of Subjects	True ORR					
	0.1		0.3		0.5	
	No Go	Go	No Go	Go	No Go	Go
5	0%	8%	0%	47%	0%	81%
10	35%	11%	3%	67%	0%	96%
15	35%	13%	3%	77%	0%	99%
20	48%	13%	3%	79%	0%	99%
25	60%	13%	4%	83%	0%	100%
30	60%	13%	4%	85%	0%	100%
35	65%	13%	4%	86%	0%	100%
40	70%	13%	4%	87%	0%	100%
45	70%	13%	4%	89%	0%	100%
50	73%	13%	4%	90%	0%	100%
55	76%	13%	4%	90%	0%	100%
60	76%	13%	4%	91%	0%	100%

ORR = objective response rate.
Numbers are for demonstration purpose. The actual sample size per tumor type at each look will depend on tumor type distribution

Table 5. Cumulative Probability of Go/No Go for CRC Subjects

Number of Subjects	True ORR					
	0.05		0.15		0.25	
	No Go	Go	No Go	Go	No Go	Go
5	0%	23%	0%	56%	0%	76%
10	0%	40%	0%	80%	0%	94%
15	0%	41%	0%	84%	0%	96%
20	0%	45%	0%	89%	0%	99%
25	0%	46%	0%	91%	0%	99%
30	21%	47%	1%	93%	0%	100%
35	21%	48%	1%	94%	0%	100%
40	21%	48%	1%	95%	0%	100%
45	21%	48%	1%	96%	0%	100%
50	21%	48%	1%	96%	0%	100%
55	28%	49%	1%	96%	0%	100%
60	28%	49%	1%	96%	0%	100%

ORR = objective response rate.
Numbers are for demonstration purpose. The actual sample size per tumor type at each look will depend on tumor type distribution.

Based on emerging clinical efficacy data, the number of subjects with specific tumor types may be restricted/specified in the expansion part.

The DLRT may also recommend that additional subjects be enrolled at this estimated monotherapy RP2D or that a dose reduction or alternate dosing regimen be explored before proceeding to phase 2. The decision to proceed to the phase 2 monotherapy will be based on the totality of data from both exploration and expansion parts of the study.

A final estimate of the MTD and/or RP2D using BLRM will be evaluated and confirmed utilizing all DLT-evaluable subjects from the dose exploration and the dose expansion cohorts.

7.1.3 Phase 2

7.1.3.1 Safety

A data review team (DRT), internal to Amgen but external to the study team, will assess safety after approximately 30, 50, 70, and 100 subjects have been treated for 21 days. Based on their reviews, the DRT will make recommendations to Amgen regarding the continuation of the study. There will be no formal guidelines to stop for safety. The DRT will consist of 3 or more members including 2 or more clinicians with relevant specialties

and 1 or more statisticians. The DRT will be supported by an independent statistician who is responsible for preparing reports that describe the ongoing clinical study data. Details regarding the responsibilities of the DRT and the independent statistician will be described in the DRT Charter.

7.1.3.2 Futility

The DRT will also oversee futility analyses performed by tumor type and based on the phase 2 ORR analysis set. The interim futility analyses will be conducted in a continuous manner using Bayesian predictive probability (Lee and Liu, 2008) for NSCLC and CRC separately. Interim futility analysis will be performed by tumor types (NSCLC, CRC). For NSCLC subjects, it will begin after approximately 25 response-evaluable subjects, defined as received at least 1 dose of AMG 510 and have had at least 6 weeks response data starting from day 1. For CRC subjects, it will begin after approximately 20 response-evaluable subjects. Subjects who stopped disease assessments prior to 6 weeks will be included in this analysis if the data cutoff is at least 6 weeks after their first dose date. Following this initial interim analysis, for each tumor type, subsequent interim analyses will be performed after every 10 subjects in each tumor type becomes response evaluable.

The Go criterion will be met if the probability that the true ORR exceeds the benchmark ORR is ≥ to a high probability of:

Go Criterion for NSCLC: probability [ORR > 0.23] ≥ 80%

Go Criterion for CRC: probability [ORR > 0.1] ≥ 95%

Given the existing observed data during the continuous monitoring stage, the Bayesian predictive probability is obtained by calculating the probability of reaching a Go Criterion should the treatment group be enrolled and evaluated to the maximum planned final sample size of 105 NSCLC subjects and 60 CRC subjects. The Go criterion is for interim futility analysis purpose only.

Futility will be met if it is predicted that there is a small probability of reaching a Go Criterion upon full enrollment of 105 NSCLC subjects and 60 CRC subjects given the existing observed data. A noninformative prior distribution of beta (1, 1) will be used.

Futility NSCLS: Predictive probability of a Go decision < 5%

Futility CRC: Predictive probability of a Go decision < 30%

Further enrollment may be terminated if futility is met. The futility analyses will be based on site-assessed disease response and the futility rules will be nonbinding. Due to the efficacy already observed in NSCLC during dose escalation phase, there will be no enrollment pause for NSCLC during the futility analyses. Enrollment will be paused for CRC at the first interim futility analysis and may be paused at the subsequent interim analyses upon DRT's recommendation.

The decision rule and operating characteristics for continuous monitoring of ORR in NSCLC subjects and CRC subjects are provided in Table 6 and Table 7, respectively. For example, observing 3 or fewer observed responders after 25 NSCLC subjects have become evaluable would be considered futile due to a small probability of reaching a Go Criterion upon full enrollment of 105 subjects given the existing observed data.

Table 6. Stopping Boundary and Operating Characteristics in NSCLC Subjects

Number of Subjects	Considered Futile If Observing Number of Responses	Cumulative Probability of Futility					
		True ORR=0.1	True ORR=0.2	True ORR=0.3	True ORR=0.4	True ORR=0.5	True ORR=0.6
25	≤ 3	76%	23%	3%	0.2%	0.0%	0.0%
35	≤ 5	89%	32%	4%	0.3%	0.0%	0.0%
45	≤ 7	94%	39%	5%	0.3%	0.0%	0.0%
55	≤ 10	98%	51%	6%	0.3%	0.0%	0.0%
65	≤ 13	100%	63%	8%	0.3%	0.0%	0.0%
75	≤ 16	100%	73%	10%	0.3%	0.0%	0.0%
85	≤ 19	100%	80%	12%	0.4%	0.0%	0.0%
95	≤ 22	100%	85%	14%	0.4%	0.0%	0.0%
105	≤ 27	100%	94%	23%	0.5%	0.0%	0.0%
Average Number of Subjects		29	60	99	105	105	105

NSCLC = non-small cell lung carcinoma; ORR = objective response rate

Table 7. Stopping Boundary and Operating Characteristics in CRC Subjects

Number of Subjects	Considered Futile If Observing Number of Responses	Cumulative Probability of Futility					
		True ORR=0.05	True ORR=0.1	True ORR=0.15	True ORR=0.2	True ORR=0.25	True ORR=0.3
20	≤ 2	92%	68%	41%	20%	9%	4%
30	≤ 3	96%	75%	45%	23%	10%	4%
40	≤ 5	99%	85%	55%	27%	11%	4%
50	≤ 7	100%	92%	63%	32%	12%	4%
60	≤ 9	100%	95%	70%	35%	13%	4%
Average Number of Subjects		21	28	40	50	56	58

CRC = colorectal cancer; ORR = objective response rate

7.2 Primary Analysis

7.2.1 Phase 1

The primary analysis for phase 1 will occur when target enrollment in phase 1 dose escalation and dose expansion is complete and each subject either completes 6 months on study or withdraws from the study.

7.2.2 Phase 2

The primary analysis for phase 2 will occur after 105 NSCLC or 60 CRC subjects are enrolled in phase 2 and have 6-month follow-up, whichever group occurs first. The data cutoff was decided to allow sufficient time to demonstrate durability of ORR. Subjects who end the study prior to 6 months will be counted. The data will be analyzed once they have been entered, cleaned, and locked. The primary analysis will summarize for all tumor types even if it is triggered by 105 NSCLC subjects or 60 CRC subjects. Results from the tumor cohort without sufficient subjects with 6-month follow up will be used descriptively. A subsequent analysis when the prespecified number of subjects in this cohort reach 6 months follow-up is outlined in Section 7.3.2.

7.3 Additional Analysis Subsequent to Primary Analysis

7.3.1 Phase 1

At the time of Phase 2 Primary Analysis, phase 1 analyses will be updated to capture additional durable response after Phase 1 Primary Analysis.

7.3.2 Phase 2

If the primary analysis is triggered by 105 NSCLC (60 CRC) subjects reaching 6-month follow-up, a subsequent analysis will occur when 60 CRC (105 NSCLC) subjects have 6-month follow-up. The data will be analyzed once they have been entered, cleaned, and locked.

7.4 Final Analysis

The final analysis will occur when the end of study as defined in Section 5 has been reached. The data will be analyzed once they have been entered, cleaned, and locked. The purpose of this analysis is to summarize efficacy and safety after all subjects have completed follow-up.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database. The database will be subject to edit checks outlined in the Clinical Data Management Plan (DMP). See details of this section in the DMP.

8.3 Handling of Missing and Incomplete Data

Incomplete adverse event and concomitant medication dates missing data will be imputed as described in Appendix A.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in each cohort. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

PK concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard PK evaluation practice.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required data transformations of analyses will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographic, safety and efficacy data. Descriptive statistics on continuous data will include means, medians, standard deviations, minimums & maximums while categorical data will be summarized using frequency counts and percentages. For time-to-event variables, the Kaplan-Meier (KM) estimates and corresponding two-sided 95% confidence intervals for the median and quartiles will be provided. Graphical summaries of the data may also be presented. The K-M plot may also be provided.

Efficacy and safety analyses will pool together all tumor types and also present tumor types separately. Efficacy analysis for Phase 1 and Phase 2 will be analyzed separately. In addition, integrated safety analyses will be done by different planned dose levels and treatments (monotherapy or combination therapy) and phases, using the Safety Analysis Set.

Futility and efficacy thresholds in phase 1 and futility interim in phase 2 will be based on site-assessed disease response per RECIST 1.1. Primary, final, and any additional efficacy analyses will be based on an independent radiologic assessment of disease response per RECIST 1.1.

Nominal 95% confidence intervals will be calculated.

9.2 Subject Accountability

The number and percent of subjects who were enrolled, received investigational product, discontinued from investigational product (including reasons for discontinuing, completed study, discontinued the study (including reasons for discontinuing) will be summarized. Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the study. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations will be provided.

9.4 Demographic and Baseline Characteristics

The following descriptive summaries of the demographic and baseline characteristics will be produced:

- Race: (White, Asian, Black or African American, vs other categories depending on frequency observed) If multiple races have been reported for a subject, the subject will be categorized as multiple.
- Gender: (male vs. female)
- Age at enrollment categories (< 65 vs. $\geq$ 65)
- Age at enrollment in years (summary statistics)
- Baseline weight (summary statistics)
- ECOG Performance Status at baseline (0 vs. 1)
- Time from initial diagnosis to enrollment
- Primary tumor location (NSCLC, CRC vs other tumor types)
- Disease Stage at Initial Diagnosis (I, II, III, IV)
- Disease Stage at Screening (I, II, III, IV)
- Histopathology Type (Adenocarcinoma, squamous cell carcinoma, Large cell carcinoma, Bronchoalveolar carcinoma, undifferentiated, other)
- Prior lines of therapy (0, 1, 2)
- Prior anti-cancer therapy for current malignancy (yes, no)
- Response to prior anti-cancer (yes, no)
- Prior radiotherapy for current malignancy (yes, no)
- Prior surgery for current malignancy (yes, no)

- Number of metastatic sites (0,1, 2 or more)
- Brain metastases (yes, no)
- Liver metastases (yes, no)
- History of tobacco use (yes, no)
- ECHO or MUGA, if available

9.5 Efficacy Analyses

Table 8. Phase 1 Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Analysis Set	Sensitivity Analysis
Primary Endpoint			
None	-	-	-
Secondary Endpoint			
ORR	The percentage of subjects with an OR will be summarized along with a Clopper-Pearson exact confidence interval. Subjects without a post-baseline tumor assessment will be considered non-responders.	Interim during dose expansion: P1OAS Primary and Final: P1FAS	None
DOR	Kaplan-Meier quartiles and rates for select durations (eg, > 3, > 6, > 9, > 12 months)	P1FAS	None
DCR	The percentage of subjects with disease control will be summarized along with a Clopper-Pearson exact confidence interval. Subjects without a post-baseline tumor assessment will be considered non-responders.	P1FAS	None
Duration of stable disease	Kaplan-Meier quartiles and rates for select durations (eg, > 3, > 6, > 9, > 12 months)	P1FAS	None
PFS	Kaplan-Meier curves, quartiles, and rates for select timepoints (eg, 6 and 12 months)	P1FAS	None

P1OAS = Phase 1 monotherapy RP2D ORR Analysis Set. P1FAS = Phase 1 Full Analysis Set

Table 9. Phase 2 Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Analysis Set	Sensitivity Analysis
Primary Endpoint			
ORR	The percentage of subjects with an OR in Phase 2 ORR Analysis Set will be summarized along with a Clopper-Pearson exact confidence interval. Subjects without a post-baseline tumor assessment will be considered non-responders.	P2OAS	None
Secondary Endpoints			
DOR	Kaplan-Meier quartiles and rates for select durations (eg, > 3, > 6, > 9, > 12 months)	P2OAS	None
DCR	The percentage of subjects with disease control will be summarized along with a Clopper-Pearson exact confidence interval. Subjects without a post-baseline tumor assessment will be considered non-responders.	P2FAS	None
OS	Kaplan-Meier curves, quartiles, and rates for select timepoints (eg, 6 and 12 months)	P2FAS	None
PFS	Kaplan-Meier curves, quartiles, and rates for select timepoints (eg, 6 and 12 months)	P2FAS	None
TTR	Summary of non-missing sample size (n), mean, standard deviation, median, minimum, and maximum for responders	P2OAS	None

P2OAS = Phase 2 ORR Analysis Set. P2FAS = Phase 2 Full Analysis Set

9.5.1 Analyses of Primary Efficacy Endpoint(s)

The number and percentage of subjects with a best overall response of Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Evaluable (NE) will be presented. ORR will be summarized along with a Clopper-Pearson exact 95% confidence interval (Clopper and Pearson, 1934). Subjects without a post-baseline tumor assessment will be considered non-responders.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

DOR will be calculated only for subjects who achieve a best overall response of PR or better. Subjects will be censored following the censoring strategy described in the definition of PFS time in Table 1. The distribution of DOR, including the median and quartiles will be characterized using the Kaplan-Meier(KM) method based on the subjects who achieve a best response of PR or better. The 95% CIs for the median and

quartiles of PFS will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The rates for select durations (eg, > 3, > 6, > 9, > 12 months) will be reported. The 95% CIs for PFS rates will be estimated using the methods by Kalbfleisch and Prentice (1980) with log-log transformation. KM curve can be done for DOR if at least 10 subjects have a CR/PR.

The proportion of subjects with disease control (CR, PR or SD> 6 weeks) with corresponding exact 95% CI will be calculated using the Clopper-Pearson method.

Duration of Stable Disease will be analyzed using the same method as describe for DOR.

The distribution of PFS, including median, will be estimated using the Kaplan-Meier method. PFS rate at the selected time points (6 months and 12 months) will be reported. The 95% CIs for the median and other percentiles of PFS will be constructed using the method of Klein and Moeschberger (1997) with log-log transformation. The 95% CIs for PFS rates will be estimated using the methods by Kalbfleisch and Prentice (1980) with log-log transformation.

OS will be analyzed using the same method as describe for the PFS endpoints.

Time to response will be summarized with the non-missing sample size (n), mean, standard deviation, median, minimum, and maximum for responders, ie, subjects who achieve best overall response of sCR, CR, BGPR, or PR.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

PFS2 is defined as time from start of the treatment to objective disease progression on next-line treatment or death from any cause, whichever occurs first. If the date of the second disease progression is not available, then the start date of the next line of therapy following the second disease progression will be used as the surrogate for the date of the second disease progression and it will be considered as a PFS2 event. For a subject who is alive and without second disease progression date or the start date of the next line of therapy, PFS2 will be right-censored at the date on which the subject is last known to be alive. The analysis method will be the same as that for the PFS and OS analysis.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Unless otherwise specified, statistical analyses on safety endpoints in Phase 1 will be done using subjects from the Phase 1 Full Analysis Set; statistical analyses on safety

endpoint in Phase 2 will be done using subjects from the Phase 2 Full Analysis Set; integrated safety analysis will be done using subjects from integrated Safety Analysis Set, which includes all subjects that are enrolled and received at least 1 dose of AMG 510. DLT analysis will be done using DLT-evaluable subjects.

Subject incidence of DLTs will be used to fit the BLRM model to estimate the probability of having a DLT across dose levels

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and death due to adverse events.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order.

The number and percentage of subjects reporting adverse events will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.

The severity of each adverse event will be graded using The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria.

- **http://ctep.cancer.gov/protocolDevelopment/electronicapplications/ctc.htm.**

Summaries of treatment-emergent and serious adverse events will be tabulated by system organ class, preferred term, and grade.

9.6.3 Laboratory Test Results

Laboratory data will be summarized using standard descriptive statistics at each scheduled time point in the study. For continuous parameters, a summary of the changes from baseline to each post dose laboratory assessment will also be produced. Shifts in selected laboratory parameters between baseline and the worst on-study value will be summarized according to the NCI CTCAE toxicity grades. Safety Laboratory collection includes chemistry, hematology, pregnancy test (for women of child-bearing potential) either urine or serum, and urine albumin-creatinine ratio

The parameters described in Table 7 of the protocol will be collected, converted to Amgen standard units and summarized.

Selected individual analytes will be summarized by cohort using standard descriptive statistics at each of the scheduled time points through the study up to the safety follow-up visit. For continuous parameters, a summary of the changes from baseline to each post-dose laboratory assessment will be produced for each cohort.

Tables of shifts from baseline to the worst-case on-study increased and decreased values (graded according to the NCI Common Toxicity Grading Criteria) will be provided for selected laboratory parameters with available NCI-CTCAE grades. Unscheduled assessments will be included in the shift tables.

Subject incidence of suspected Hy's law cases (Hy's law predicts potential for drug-related hepatotoxicity) will be summarized by cohort. A listing of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin values at each time point will be produced for the subjects suspected of Hy's law case.

Boxplots may be plotted by time point and cohort for selected analytes.

9.6.4 Vital Signs

Vital signs data (eg, systolic / diastolic blood pressure, heart rate, respiratory rate, temperature and pulse oximetry) will be summarized using descriptive statistics. Summary statistics for each vital sign parameter will be provided for baseline and each scheduled post-baseline assessment. Depending on the size and scope of changes, summaries of changes from baseline over time may be provided. Unscheduled assessments will be included in this summary.

Shifts in scores for ECOG performance status scores between the baseline and each assessed time point will be tabulated. ECOG performance status scores will be summarized at relevant time points.

9.6.5 Physical Measurements

Physical measurement data will be listed and reviewed for each subject. Depending on the size and scope of changes, summaries of changes from baseline over time may be provided. Unscheduled assessments will be included in this summary.

9.6.6 Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

Subjects' maximum change from baseline in QT interval corrected by Fridericia's formula will be categorized and the number and percentage of subjects in each group will be summarized. Unscheduled assessments will be included in the determination of the maximum change. The categories are <= 30 msec, > 30 – 60 msec, > 60 msec.

Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized. The categories are <= 450 msec, > 450 – 480 msec, > 480 – 500 msec, > 500 msec.

All on-study ECG data will be presented and select parameters of interest may be plotted.

In addition, the relationship between AMG 510 exposure and change from baseline in QTc will be explored graphically. More details on analyses of ECG data are available in Supplemental Statistical Analysis Plan for ECGs Analyses.

9.6.7 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by cohorts, combining data for each study part. Number of cycles started, number of doses of investigational product, the cumulative dose by unit and average dose delivered per day, relative dose intensity will be summarized. Summaries of the number and percentage of subjects with dose modifications and reason for modification will be provided.

[redacted]

9.6.9 Exposure to Other Protocol-required Therapy

Not applicable.

9.6.10 Exposure to Concomitant Medication

The number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category as coded by the World Health Organization Drug (WHO DRUG) dictionary.

9.7 Other Analyses

Other analyses in the study include analyses for PK endpoints, PRO, and biomarker endpoints.

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Phase 1:

Nominal sampling times will be used for individual concentration-time plots and tables. Actual dose administered, and actual sampling times will be used for the calculation of PK parameters for each subject. The reasons for excluding any sample from the analyses will be provided.

Individual concentration-time data will be tabulated and presented graphically. Summary of PK concentration over time and PK parameters will be provided. Mean concentration-time profiles for each dose will be provided.

PK parameters will include, but are not limited to, maximum observed concentration (C_{max}), time to maximum concentration (t_{max}) and area under the plasma concentration-time curve (AUC). Other PK parameters such as AUC from time 0 to the time extrapolated to infinity (AUC_{inf}), apparent clearance (CL/F), and terminal half-life ($t_{1/2}$) may be analyzed. Pharmacokinetic parameters will be estimated using standard non-compartmental approaches based on the PK Analysis Set and summarized by dose level using descriptive statistics including, but not limited to means, standard deviations, medians, minimums, and maximums. Above analyses will be conducted by Amgen Clinical Pharmacology Modeling and Simulation (CPMS).

For the food-effect assessment, PK parameter estimates will help assess the impact of food on the pharmacokinetics of AMG 510. The geometric means and 90% confidence interval for the ratio of the geometric means (fed state/fasted state) will be estimated using a mixed-effects model. The model will use the log-transformed PK parameters as the dependent variable (or response) and treatment conditions (fed versus fasted) as the independent variable.

Phase 2:

For AMG 510, PK parameters (eg, C_{max}, t_{max} and AUC) will be determined where possible. 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

9.7.2 Analyses of Clinical Outcome Assessments

Clinical outcome assessment will be collected to subjects enrolled into the Phase 2 part of the study. The questionnaires should be completed by the subject prior to any other

clinical assessments and before receiving any study medications. The details of the analyses will be specified in another Supplement SAP.

9.7.3 Analyses of Health Economic Endpoints

Not applicable.

9.7.4 Analyses of Biomarker Endpoints

Relationships between changes in tumor dynamics and above biomarkers of interest listed as exploratory endpoints will be explored. Changes in expression levels of biomarkers and their relationship to dose may also be explored. Summary statistics over time will be provided and graphical presentations may be used.

The relationship between AMG 510 exposure and related biomarkers in blood will be also explored if deemed appropriate. As appropriate, details of analysis will be provided in a supplemental analysis plan for exploratory biomarker analysis.

10. Changes From Protocol-specified Analyses

PFS2 is added as exploratory endpoint analyses.

11. Literature Citations / References

Babb J, Rogatko A, Zacks S. Cancer Phase I Clinical Trials: Efficient Dose Escalation with Overdose Control. Statistics in Medicine 1998; 17:1103-1120

Kalbfleisch, J. D. and Prentice, R. L. The Statistical Analysis of Failure Time Data, New York: John Wiley & Sons; 1980

Klein, J. P. and Moeschberger, M. L. *Survival Analysis: Techniques for Censored and Truncated Data*, New York: Springer-Verlag; 1997.

Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clinical Trials. 5(2):93-106. 2008

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008 Jun 15; 27(13):2420-39.

Clopper C.J. and Pearson E.S. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika Vol. 26, No. 4 (Dec., 1934): 404-413

12. Prioritization of Analyses

No priority of output is planned for this study.

13. Data Not Covered by This Plan

The analysis of Biomarkers and PRO endpoints is not covered in this plan.

14. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or con-med stopped and the stop date will be imputed, if partial.

Imputation Rules for Partial or Missing Start Date:

		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		
Start Date		< 1st Dose	≥ 1st Dose	< 1st Dose yyyymm	≥ 1st Dose yyyymm	< 1st Dose yyyy	≥ 1st Dose yyyy	Missing
Partial: yyyymm	= 1st Dose yyyymm	2	1	2	1	N/A	1	1
	≠ 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	= 1st Dose yyyy	3	1	3	1	N/A	1	1
	≠ 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first of the month

3 = Impute January 1 of the year

4 = Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Appendix B. Code Fragments

Provisional Code Fragments for calculating a confidence interval using the Clopper Pearson Method. The following example SAS code will be utilized for the response rate analysis providing the proportion of subjects responding to treatment with corresponding 95% confidence intervals and 90% confidence intervals.

For 95% confidence intervals:

```
data propci (keep = ns p low_ci upp_ci);
n=xx; * total n within the treatment group;
ns= xx; *number of responders;
p=ns/n; * response rate;
q=1-p;
lowF=FINV(0.025, 2*ns, 2*(n-ns+1)); /* use for 2-sided 95% CI */
UppF=FINV(1-0.025, 2*(ns+1), 2*(n-ns)); /* use for 2-sided 95% CI */
low_ci = 1 / (1+(n-ns+1) / (ns*lowf)); * lower CI for response rate;
upp_ci = 1 / (1+(n-ns) / ((ns+1)*uppf)); *upper CI for response rate;
if p=1 then upp_ci=1;
if p=0 then low_ci =0;
output;
end;run;
```

For 90% confidence intervals.

```
data propci (keep = ns p low_ci upp_ci);
n=xx; * total n within the treatment group;
ns= xx; *number of responders;
p=ns/n; * response rate;
q=1-p;
lowF=FINV(0.05, 2*ns, 2*(n-ns+1)); /* use for 2-sided 90% CI */
UppF=FINV(1-0.05, 2*(ns+1), 2*(n-ns)); /* use for 2-sided 90% CI */
low_ci = 1 / (1+(n-ns+1) / (ns*lowf)); * lower CI for response rate;
upp_ci = 1 / (1+(n-ns) / ((ns+1)*uppf)); *upper CI for response rate;
if p=1 then upp_ci=1;
if p=0 then low_ci =0;
output;
```

Summary of Changes SAP Amendment 1

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	14NOV2018	Original SAP
Amendment 1 (v2.0)	16JUL2019	Add phase 2 portion and analyses per Protocol Amendment 3 (22 May 2019)