

Title Page

Protocol Title:		A Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 256 in Patients With Advanced Solid Tumors	
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

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Investigator's Agreement:

I have read the attached protocol entitled A Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 256 in Patients with Advanced Solid Tumors, dated 20 March 2020, and agree to abide by all provisions set forth therein.

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

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

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

Signature

Name of Investigator

Date (DD Month YYYY) _____

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 256 in Patients with Advanced Solid Tumors

Short Protocol Title: AMG 256 in Patients with Advanced Solid Tumors

Study Phase: 1

Indication: Advanced Solid Tumors

Rationale

Extensive clinical experience has shown clinical benefit of checkpoint inhibitors, primarily PD-1 and PD-L1 inhibitors across many tumor types. However, many patients require additional (concurrent or sequential) treatments to either maximize the benefit of such drugs or overcome resistance after an initial benefit.

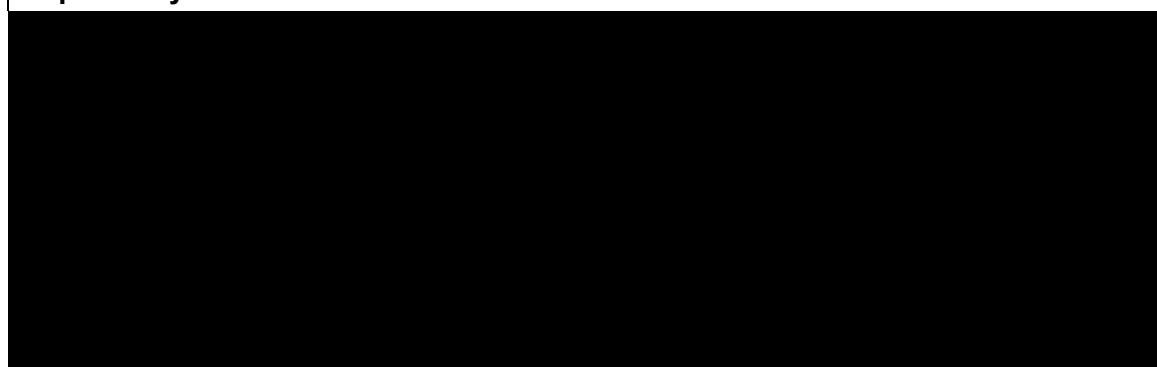
AMG 256 is a fully human bifunctional fusion protein, consisting of a bivalent PD-1 antibody fused to a monomeric IL-21 mutein. The IL-21 cytokine in the fusion protein has been mutated to diminish its affinity for IL-21R compared to the wild type protein; this modification serves to reduce the stimulation of cells that express IL-21R and specifically activate only when PD-1 component is engaged. Co-expression of IL-21R and PD-1 on immune cells enables the binding of the anti-PD-1 antibody portion of the fusion protein allowing for a more stable interaction between the IL-21 mutein domain and IL-21R which leads to the activation of the IL-21 pathway. In addition to serving as a means of directing AMG 256 to PD-1-expressing cells, the anti-PD-1 antibody portion of the fusion protein blocks the interaction between PD-1 and ligands PD-L1/L2, thereby releasing the inhibitory signal that resulted from the interaction. The combination of PD-1 blockade with IL-21 signaling at the T cell level may enhance T cell function in cancer and improve anti-tumor immunity but, based on IL-21R-mediated activity only in the context of PD-1 binding, with potentially minimal additional toxicity beyond anti-PD1 monotherapy.

This first-in-human AMG 256 study is designed to assess safety and tolerability of AMG 256 monotherapy in patients with solid tumor malignancies.

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Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of AMG 256 in adult subjects with advanced solid tumors	Dose limiting toxicities (DLTs), treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, and clinical laboratory tests
To estimate the maximum tolerated dose (MTD) and/or biologically active dose (eg, recommended phase 2 dose [RP2D]) within investigated subject population groups	MTD and/or RP2D
Secondary	
To evaluate the pharmacokinetics (PK) of AMG 256	PK parameters of AMG 256 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 the preliminary antitumor activity of AMG 256	- Objective Response (OR), per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (RECIST) 1.1 and iRECIST - Duration of Response (DOR) - Progression-free survival (PFS), 6-month and 1-year PS - Disease Control Rate (DCR) - Duration of stable disease - Overall Survival (OS), 1 and 2- year
To assess the immunogenicity of AMG 256	Subject incidence of anti-AMG 256 antibodies
Exploratory	



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Overall Design

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study to evaluate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AMG 256 in subjects with advanced solid tumors. AMG 256 will be administered by intravenous (IV) infusion on [REDACTED] cycle or [REDACTED] and [REDACTED] of [REDACTED] cycle. The study may be conducted in Australia, Belgium, United Kingdom, United States, Poland, Japan and China. Other countries or regions may participate. The study will be conducted in 2 parts: Part 1 – Dose Escalation and Part 2 – Dose Expansion. Part 1 is intended to evaluate the safety, tolerability, PK and PD of AMG 256 and determine the maximum tolerated dose (MTD) in subjects with advanced solid tumors using a Bayesian Logistics Regression Model (BLRM) design. Part 2 will further evaluate the safety of the MTD and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) in specific tumor types. The dose expansion part of the study (Part 2) can be opened once the MTD/RP2D has been determined in Part 1. The dose escalation part of the study will consist of approximately 40 subjects and the dose expansion will consist of approximately 60 additional subjects. Dose escalation will be conducted in checkpoint inhibitor-naïve subjects; and dose expansion will be conducted in checkpoint inhibitor-exposed subjects with specific tumor types. The DLT evaluation period will be [REDACTED]. Based on emerging clinical efficacy data, the cancer types explored in the expansion part may be modified. Administration of AMG 256 (in part 1 and part 2) may continue until evidence of disease progression, intolerance to study medication, withdrawal of consent, or in the absence of the above up to 12 months if a subject achieves a complete response, and up to 24 months if partial response or stable disease is achieved.

Dose Escalation – Part 1

Dose escalation cohorts will estimate the safety, tolerability, PK, and PD of different doses of AMG 256 in subjects with advanced solid tumors who have not received treatment previously with a checkpoint inhibitor. Subjects will receive AMG 256 [REDACTED] [REDACTED] or [REDACTED]. Dose escalation will begin with [REDACTED] dosing and [REDACTED] dosing will begin as indicated in the Study Schema (Figure 1-1). The [REDACTED] dosing may be initiated at lower doses or later than indicated, based on emerging safety, PK and/or preliminary response data. Dose escalation will begin with single subject cohorts treated at the lowest planned dose level of [REDACTED] mg [REDACTED]. The cohort size will be increased to N = 2-4 subjects after observation of treatment-related adverse events of

grade 2 or higher; or escalation has reached the presumed efficacious dose; or is recommended by the dose level review team (DLRT) to further evaluate a cohort.

To minimize the number of subjects treated at potentially toxic dose levels, subjects in each multiple subject cohort will be enrolled sequentially ([Section 11.10](#)).

- During dose escalation, [REDACTED] dosing subjects will be sequentially enrolled with a minimum of [REDACTED] between the first and second subjects being dosed within a cohort; and a minimum of 1 day between the second, third and fourth subjects being dosed within a cohort.
- During dose escalation, [REDACTED] dosing subjects will be enrolled with a minimum of [REDACTED] between the first and second being dosed within a cohort; and a minimum of 1 day between the second, third and fourth subjects within a cohort.

The sequential dosing of subjects within a cohort should be maintained as best possible for the [REDACTED] of treatment to minimize the potential for multiple subjects experiencing hypersensitivity reactions on the same day. The goal of the sequential dosing is to avoid multiple subjects receiving the same dose number on the same day during the first two cycles (ie, two subjects receiving [REDACTED] dose on the same day).

Dose escalation will follow the planned Study Schema schedule. If no DLT is observed, dose escalation will continue to the next planned dose cohort as per the Study Schema. 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 DLRT using the dose level recommendation from the BLRM, as appropriate, and by evaluating all available safety data, including late onset immune-mediated toxicities, laboratory data, and PK information.

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

- The subject has not experienced any clinically significant $\geq$ grade 2 adverse events (deemed treatment related by the investigator) during treatment

Subjects who do not proceed to a higher dose may continue to receive additional cycles at the original dose. Dose escalation will continue until any of the following events:

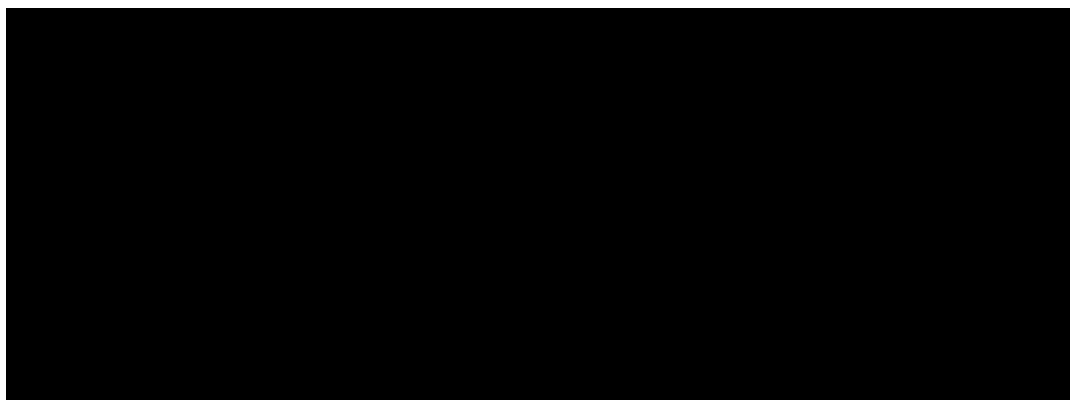
- The highest planned dose level is determined to be safe and tolerable (minimum of 6 DLT-evaluable subjects)
- The MTD is identified, BLRM recommends a dose level which already has 6 DLT-evaluable subjects

Additional subjects (up to 10) 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 used to better estimate the RP2D and better characterize the safety, efficacy, pharmacokinetics and pharmacodynamics of AMG 256 and may be concurrent with dose escalation to identify the MTD.

Dose Expansion – Part 2

Upon completing the dose escalation part of the study and depending on data obtained, dose expansion may proceed. The RP2D/MTD will be administered in the dose expansion. Dose expansion will open to 2 groups with certain advanced solid tumors that are checkpoint-inhibitor exposed, as indicated below.

The first 6 subjects enrolled during expansion will be enrolled sequentially, with a minimum of 2 days between the subjects initiating treatment.



Dose expansion in all groups may be done concurrently.

Number of Subjects

Part 1 – Dose Escalation: Up to 30 evaluable subjects may be enrolled in the dose escalation part of the study with a maximum of 10 subjects enrolled by backfill enrollment.

Part 2 – Dose Expansion: An additional 60 evaluable subjects will be enrolled in the dose expansion part of the study, which will be conducted in 2 groups. Up to 40 subjects will be enrolled to group 1 and up to 20 subjects in group 2.

Summary of Subject Eligibility Criteria

Adult subjects (≥ 18 years old) with histologically or cytologically proven metastatic or locally advanced solid tumors not amenable to curative treatment with surgery or radiation for which no standard therapy exists, standard therapy has failed, or is unavailable, or in the investigator's opinion standard therapy does not result in meaningful clinical benefit will be enrolled.

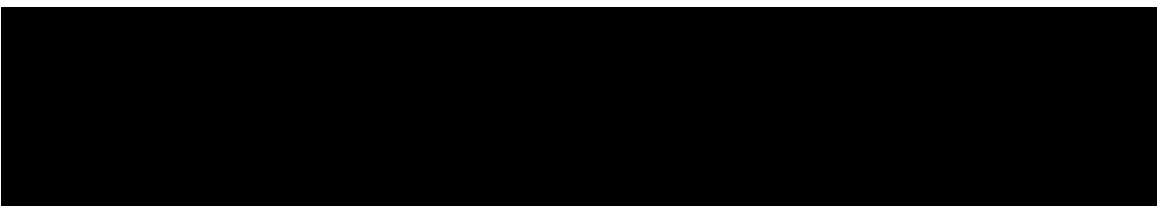
Subjects enrolled to Part 1 (Dose Escalation) must not have previously been treated with an anti-PD(L)-1 agent or other checkpoint inhibitor.

Subjects enrolled to Part 2 (Dose Expansion) must have been treated with an anti-PD(L)-1 agent and/or CTLA-4.

For a full list of eligibility criteria, please refer to [Section 5.1](#) to [Section 5.2](#).

Treatments

AMG 256 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.



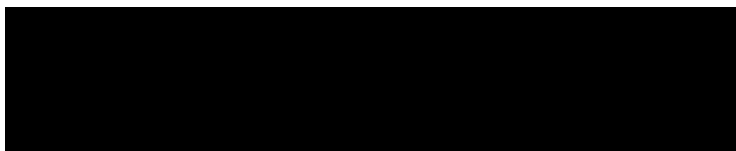
AMG 256 solution for intravenous infusion will be prepared for IV infusion and delivered through infusion lines using a syringe pump (Cohorts 1-3) and preprogrammed infusion pumps (Cohorts 4 and above) approved for use in the country in which the subject is undergoing treatment.

For multi-subject cohorts in dose escalation, sites must receive written confirmation from the study team prior to all doses during cycles 1 and 2 with approval that it is safe to proceed with dosing.

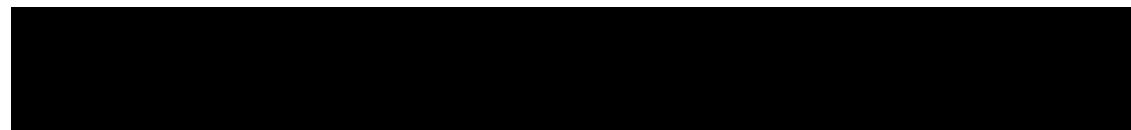
During cycles 1 and 2 for multi-subject cohorts in dose escalation, sites must notify the study team when a subject has been dosed and if subject experienced any significant adverse reaction (ie, infusion-related reaction or hypersensitivity reaction).

Each participating site should avoid treating more than one subject on the same day during cycles 1 and 2 to minimize the potential for multiple subjects experiencing hypersensitivity reactions on the same day.

During escalation, AMG 256 will be administered over:



During expansion, AMG 256 will be administered:



AMG 256 will be administered either on [REDACTED] cycle or [REDACTED] cycle.

The medical staff must closely observe patients for signs of anaphylaxis or any other potential adverse events.

During escalation, subjects will be observed for a minimum:

- [REDACTED] after each dose during cycles 1 and 2
- [REDACTED] after each dose during cycle 3 and all subsequent cycles

During expansion, subjects will be observed for a minimum:

- For the first 6 subjects enrolled: [REDACTED] after each dose during cycle 1 and [REDACTED] after each dose beginning with cycle 2 and all subsequent doses
- For remaining subjects enrolled: [REDACTED] after each dose

Vital signs (blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature) should be checked and recorded as per the Schedule of Activities ([Section 1.3](#)).

Subjects should be treated and observed in an area with resuscitation equipment and other agents (epinephrine, intravenous corticosteroids, etc.) available. A nurse must be present in the immediate treatment area throughout the infusion and the subsequent observation period. A physician must be in close proximity to the patient treatment area. In the event that a patient experiences an allergic/hypersensitivity reaction, see [Appendix 4, Table 11-3](#) for management instructions.

At time of discharge, subjects should be instructed to report any delayed reactions or signs of bleeding to the investigator immediately. Subjects are to be given the Symptoms Review Questionnaire ([Appendix 13](#)) with instructions to review the questions listed frequently and notify the investigator immediately if any changes are noticed. It is

recommended the subjects be contacted between doses during cycles 1 and 2, to ensure compliance of monitoring symptoms presented in the questionnaire.

Procedures

After written informed consent has been obtained, all screening tests and procedures will be performed within [REDACTED] of administration of the first dose of AMG 256 ([REDACTED]) unless otherwise noted. Subjects will be seen in clinic where critical safety and study evaluations will be performed including physical examination, vital signs, clinical laboratory tests, electrocardiograms (ECGs), PK and biomarker sample collections.

Dosing with AMG 256 can continue unless the subject becomes intolerant to investigational product, the signs and symptoms of clinical progression are evident as determined by the investigator, the subject withdraws consent, or in the absence of the above up to 12 months if a subject achieves a complete response, and up to 24 months if partial response or stable disease is achieved. Tumor evaluations will occur approximately every 8 weeks from treatment initiation. Subjects may continue to receive treatment until confirmed progression of disease.

Subjects enrolled to Cohorts 6-9, 1a and 2a in escalation and expansion must have mandatory fresh tumor biopsies at screening (an archival tumor sample is acceptable if obtained within 6 months of enrollment and subject has not received any other treatment since sample was obtained) and four (+1) weeks after start of treatment. Subjects enrolled to single subject cohorts in escalation may provide an optional archived tumor sample at screening.

Routine radiological imaging (contrast-enhanced CT scans) and tumor burden assessments will be performed as outlined in the Schedule of Activities ([Section 1.3](#)). Assessment of disease response will be determined based on modified RECIST 1.1 and iRECIST guidelines ([Appendix 11](#) and [Appendix 12](#)).

Assessments during the course of the study include: clinical evaluation (physical examination, Eastern Cooperative Oncology Group [ECOG] performance status, weight), vital signs, ECG, laboratory assessments, and biomarker and PK assessments.

For a full list of study procedures, including the timing of each procedure, please refer to [Section 8.2](#) and the Schedule of Activities in [Section 1.3](#).

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 escalation 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.

The proportion of subjects with an objective tumor response (partial and complete response) and disease control rate (DCR) (partial or complete response or stable disease for $\geq$ weeks) with corresponding exact 95% CI will be calculated and tabulated. Similarly, the proportion of subjects and 95% CI will be tabulated for 1-year duration of overall response, 1-year PFS, 1-year duration of stable disease. Kaplan-Meier curve will be presented for duration of overall response, PFS, and duration of stable disease with estimates for rate and 95% CI at selected weeks if data allows.

For a full description of statistical analysis methods, please refer to [Section 9](#).

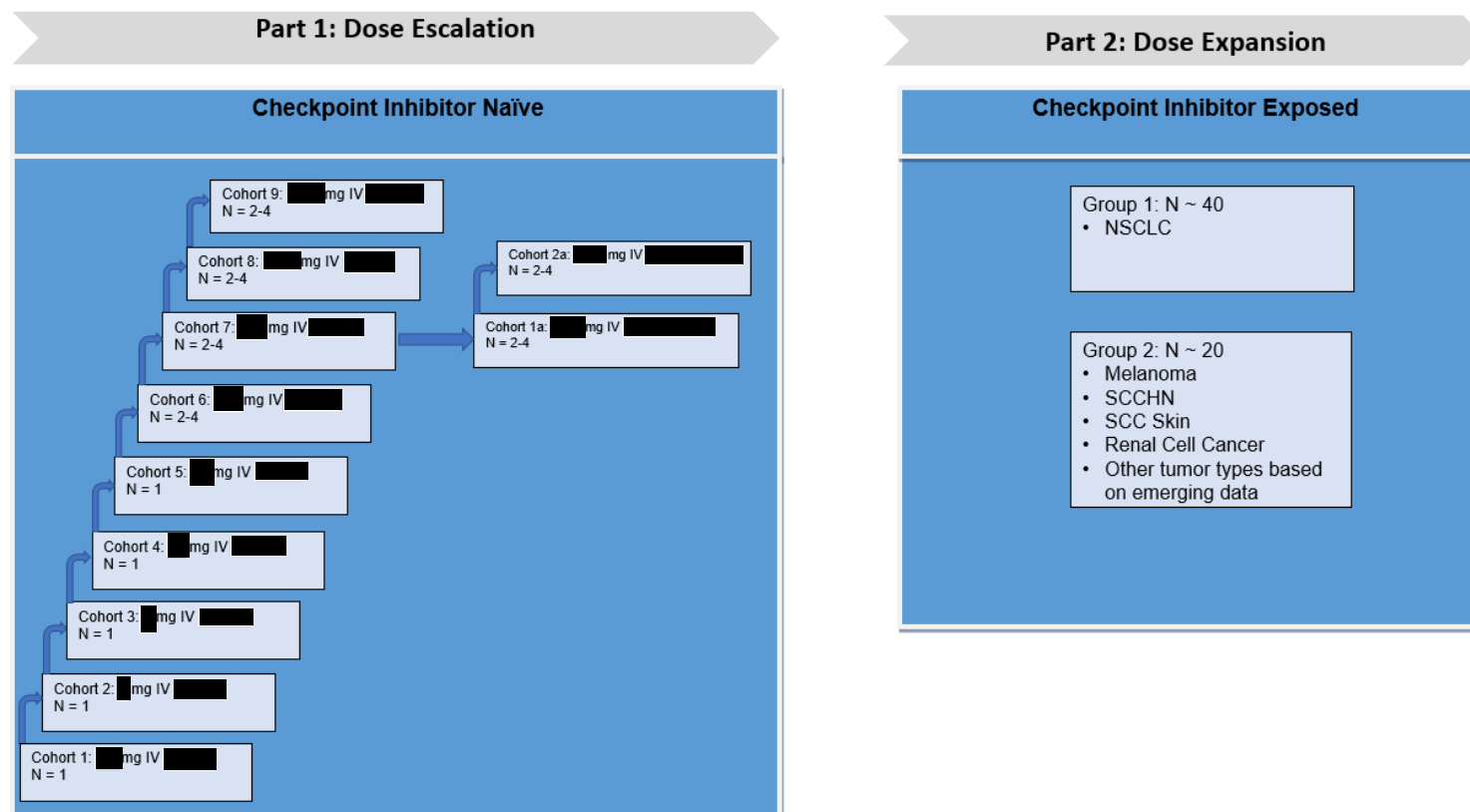
Statistical Hypotheses

This is a phase 1 study and no formal statistical hypotheses will be tested.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



Footnotes defined on next page

- The schema represented is illustrative and may change as indicated below.
- AMG 256 will be administered IV [REDACTED] as shown with the planned cohorts for [REDACTED] (Cohorts 1-9) and [REDACTED] (Cohorts 1a and 2a) dosing.
- Dose escalation will begin with single subject cohorts treated at the lowest planned dose level with [REDACTED] dosing of AMG 256. The cohort size will be increased to N= 2-4 subjects after observation of treatment-related adverse events of grade 2 or higher; or escalation has reached Cohort 6; or is recommended by the DLRT to further evaluate a cohort.
- [REDACTED] dosing schedule may be initiated in later cohorts based on emerging safety and tolerability data. the planned initial [REDACTED] dose is [REDACTED] mg [REDACTED]. [REDACTED] dosing may be initiated at doses lower than [REDACTED] mg [REDACTED] based on emerging safety, PK and/or preliminary response data from FIH study that supports anti-tumor activity with lower [REDACTED] doses.
- Dose expansion can be opened once the MTD and/or biologically active dose (eg, recommended phase 2 dose [RP2D]) has been determined in dose escalation.

Approved

Product: AMG 256
Protocol Number: 20180144
Date: 20 March 2020

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities – [REDACTED] Dosing

[illegible]

Footnotes defined on next page

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ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HIV = human immunodeficiency virus; WOCBP = Women of Child Bearing Potential

AMG 256 will be administered on [REDACTED] cycle. AMG 256 should be administered on the scheduled day ± 1 day. Pre-dose assessments must be done within 48 hours of AMG 256 infusion; screening assessments if done within 48 hours do not have to be repeated on [REDACTED] of treatment; AMG 256 will be infused after all safety assessments have been completed. **Note:** Pre-dose research samples [REDACTED] must be collected day of dosing, within 60 minutes prior to the AMG 256 infusion.

¹ Beginning with cycle 3 and subsequent cycles, physical exam is required on [REDACTED] of each [REDACTED] cycle.

² ECGs are required in triplicate run consecutively (all three ECGs should be completed within a total of five minutes from the start of the first to the completion of the third) at the following time points:

- Screening
- During escalation:

Cycle 1, [REDACTED]: predose requires 3 baseline ECGs collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (total 9 ECGs)

Cycle 1, [REDACTED] EOI and 24 (± 1) hours after EOI;

Cycle 1, [REDACTED] predose and EOI;

Beginning with Cycle 2, as clinically indicated

- During expansion, ECGs are required at screening and then as clinically indicated

³ Evaluation of vital signs and pulse oximetry is required at the following time points:

- Screening
- During escalation:

Cycle 1, [REDACTED]: predose, every 15 (± 5) minutes during the infusion at EOI, every 15 (± 5) minutes for the first 2 hours after EOI; every 30 (± 10) minutes 2-4 hours after EOI; every hour (± 15 minutes) 4-8 hours after EOI; every 4 hours (± 30 minutes) 8-24 hours after EOI

Cycle 2, [REDACTED]: predose, every 15 (± 5) minutes during infusion, at EOI, every 30 minutes (± 10) for the first 4 hours after EOI; every hour (± 15 minutes) 4-6 hours after EOI; every 6 hours (± 30 minutes) 6-24 hours after EOI

Cycle 3 and all subsequent cycles, [REDACTED] predose, every 15 (± 5) minutes during infusion, EOI, one hour (± 15 minutes) after EOI

- During expansion:

Cycle 1, [REDACTED] predose, every 15 (± 5) minutes during the infusion at EOI, every 30 (± 10) minutes for the first 4 hours after EOI; every hour (± 15 minutes) 4-6 hours after EOI

Cycle 2 and all subsequent cycles, [REDACTED]: predose, every 15 (± 5) minutes during infusion, EOI, one hour (± 15 minutes) after EOI

⁴ WOCBP, serum within 48 hours prior to cycle 1, [REDACTED]; then beginning with cycle 2 urine or serum within 48 hours of day 1 of every cycle

⁵ Coagulation to include: PT, PTT/INR, fibrinogen, D-dimer, FDP

⁶ Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN/Total urea, Calcium, Chloride, Creatinine, Direct Bilirubin, Glucose, LDH, Magnesium, Phosphate, Potassium, Sodium, Total Bilirubin, Total protein, TSH, Free T4, Uric Acid

⁷ ACTH to be evaluated at screening and prior to AMG 256 administration on day 1 of every cycle. ANA and ANCA to be evaluated at screening and then if clinically indicated.

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- ⁸ Radiologic imaging and tumor assessments are required at screening and every 8 (± 1) weeks post-therapy initiation until clinically significant disease progression or deterioration, withdrawal of consent or start of new anticancer therapy. Every assessment must include the chest, abdomen, and pelvis, all other known sites of disease and MRI of the brain if a subject has signs or symptoms suggestive of CNS metastases. The MRI/CT can be obtained earlier if clinical deterioration necessitates an earlier scan at the discretion of the treating investigator. The same contrast and modality used at screening should be used for all subsequent assessments.
- Tumor burden assessments will be performed based on modified RECIST 1.1 and iRECIST guidelines ([Appendix 11](#) and [Appendix 12](#)). To confirm disease progression, a second MRI/CT scan must be performed 4-6 weeks after the first detection of radiographical progression. If a subject continues AMG 256 treatment after confirmation of radiographic progression disease, CT/MRI assessment will be performed every 8 (± 1) weeks thereafter.
- ⁹ All subjects must have MRI of the brain performed within 28 days prior to the first dose of AMG 256. In subjects with known brain metastasis, brain MRI scans must be conducted at screening and at the same schedule as radiologic imaging and tumor assessments. Brain MRI can also be performed at any time if clinically indicated. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. The same contrast and modality used at screening should be used for all subsequent assessments.
- ¹⁰ All visible cutaneous and subcutaneous tumor lesions must be documented digitally using standardized photographic images including a ruler for scale as part of the image.
- ¹¹ Tumor markers, if applicable, are required at screening and every 8 (± 1) weeks post-therapy initiation until clinically significant disease progression or deterioration, withdrawal of consent or start of new anticancer therapy.
- ¹² AMG 256 will be administered by intravenous infusion on [REDACTED] cycle. AMG 256 should be administered on the scheduled day +1 day. See [Table 6-1](#) for infusion times.
- [REDACTED]
- [REDACTED]

- ¹⁸ Follow up visits will occur as follows:
- Safety follow up visits will occur 30 (+7) days and 90 (± 7) days after the last dose of AMG 256.
 - Long term follow-up (LTFU) phone call will be done 6 months (± 1 week) after the last dose to collect information on start of new therapies, and disease status.
- ¹⁹ Where applicable, safety blood samples should be collected at 6 hours (± 30 minutes) and 24 (± 1) hours after FOI.
- [REDACTED]

Table 1-2. Schedule of Activities – [REDACTED] Dosing

CYCLES	Screening (up to 28 days before day 1)	TREATMENT PERIOD*														TREATMENT PERIOD*				Follow-up ¹⁷																															
		1														2		3+																																	
																														EOT	SFU1 ¹⁷	SFU2 ¹⁷	LTPU ¹																		
WEEKS																																																			
DAYS																																																			
Hours (relative to end of infusion)																																																			
GENERAL AND SAFETY ASSESSMENTS																																																			
Informed Consent	X																																																		
Inclusion and exclusion criteria	X																																																		
Demographics	X																																																		
Medical History	X																																																		
Physical examination, ECOG PS, wt ¹ (ht at screening only)	X	X							X	X							X	X					X ¹			X ¹			X	X	X																				
ECG triplicate measurement ²	X	X ²	X ²			X ²			X ²	X ²																																									
Vital signs, pulse ox ³	X ³	X ³	X ³	X ³	X ³	X ³	X ³		X ³	X ³	X ³	X ³	X ³	X ³			X ³	X ³	X ³	X ³	X ³	X ³		X ³	X ³	X ³	X ³	X ³	X ³	X ³																					
Adverse events review																																																			
Serious adverse events																																																			
Concomitant medication review																																																			
LABORATORY ASSESSMENTS																																																			
Pregnancy test (WOCBP) ⁴	X ⁴	X ⁴																X ⁴											X ⁴	X ⁴	X ⁴																				
Coagulation ^{5,18}	X ⁵	X ⁵			X ⁵			X ⁵	X ⁵			X ⁵	X ⁵				X ⁵	X ⁵					X ⁵					X ⁵	X ⁵	X ⁵																					
Hematology ¹⁸	X	X			X			X	X			X	X				X	X					X					X	X	X																					
Chemistry ^{6,18}	X ⁶	X ⁶			X ⁶			X ⁶	X ⁶			X ⁶	X ⁶				X ⁶	X ⁶					X ⁶	X ⁶				X ⁶	X ⁶	X ⁶																					
HIV, Hepatitis B and C screening	X																																																		
Urinalysis	X																																																		
ACTH, ANA, ANCA ⁷	X	X ⁷															X ⁷						X ⁷					X ⁷	X ⁷	X ⁷																					
TUMOR ASSESSMENTS																																																			
Radiological imaging and tumor burden assessment ⁸	X ⁸																						X ⁸					X ⁸																							
Brain MRI/CT with contrast ⁹	X ⁹																						X ⁹					X ⁹																							
Clinical Tumor Measurements & Photography (melanoma subjects only) ¹⁰	X ¹⁰																						X ¹⁰					X ¹⁰																							
Tumor marker, if applicable ¹¹	X ¹¹																						X ¹¹					X ¹¹																							
DOSING																																																			
AMG 256 ¹²			X ¹²							X ¹²								X ¹²					X ¹²				X ¹²																								
Hospitalization			X							X								X																																	
Observation																									X				X																						
Phone Call																																																			

Footnotes defined on next page

ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HIV = human immunodeficiency virus; WOCBP = Women of Child Bearing Potential

* AMG 256 will be administered on [REDACTED] cycle. AMG 256 should be administered on the scheduled day ± 1 day. Pre-dose assessments must be done within 48 hours of AMG 256 infusion; screening assessments if done within 48 hours do not have to be repeated on [REDACTED] of treatment; AMG 256 will be infused after all safety assessments have been completed. **Note:** Pre-dose research samples [REDACTED]

[REDACTED] must be collected day of dosing, within 60 minutes prior to the AMG 256 infusion.

¹ Beginning with cycle 3 and subsequent cycles, physical exam is required on days 1 and 15 of each 28-day cycle.

² ECGs are required in triplicate run consecutively (all three ECGs should be completed within a total of five minutes from the start of the first to the completion of the third) at the following time points:

- Screening
- During escalation:

Cycle 1, [REDACTED] predose requires 3 baseline ECGs collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (total 9 ECGs)

Cycle 1, [REDACTED] EOI and 24 (± 1) hours after EOI;

Cycle 1, [REDACTED]: predose and EOI;

Beginning with Cycle 2, as clinically indicated

- During expansion, ECGs are required at screening and then as clinically indicated

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Cycle 1, [REDACTED]

Cycle 2, [REDACTED]: predose, every 15 (± 5) minutes during infusion, at EOI, every 30 (± 10) minutes for the first 4 hours after EOI; every hour (± 30 minutes) 4-6 hours after EOI; every 6 hours (± 30 minutes) 6-24 hours after EOI

Cycle 3 and all subsequent cycles, [REDACTED]: predose, every 15 minutes during infusion, EOI, one hour after EOI

- During expansion:

Cycle 1, [REDACTED]: predose, every 15 (± 5) minutes during the infusion at EOI, every 30 (± 10) minutes for the first 4 hours after EOI; every hour (± 15 minutes) 4-6 hours after EOI

Cycle 1, [REDACTED]

Cycle 2 and all subsequent cycles, [REDACTED]: predose, every 15 (± 5) minutes during infusion, EOI, one hour (± 15 minutes) after EOI

⁴ WOCBP, serum within 48 hours prior to cycle 1, [REDACTED] then beginning with cycle 2 urine or serum within 48 hours of day 1 of every cycle

⁵ Coagulation to include: PT, PTT/INR, fibrinogen, D-dimer, FDP

⁶ Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN/Total urea, Calcium, Chloride, Creatinine, Direct Bilirubin, Glucose, LDH, Magnesium, Phosphate, Potassium, Sodium, Total Bilirubin, Total protein, TSH, Free T4, Uric Acid

⁷ ACTH to be evaluated at screening and prior to AMG 256 administration on day 1 of every cycle. ANA and ANCA to be evaluated at screening and then if clinically indicated.

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⁸ Radiologic imaging and tumor assessments are required at screening and every 8 ($\pm$ 1) weeks post-therapy initiation until clinically significant disease progression or deterioration, withdrawal of consent or start of new anticancer therapy. Every assessment must include the chest, abdomen, and pelvis, all other known sites of disease and MRI of the brain if a subject has signs or symptoms suggestive of CNS metastases. The MRI/CT can be obtained earlier if clinical deterioration necessitates an earlier scan at the discretion of the treating investigator. The same contrast and modality used at screening should be used for all subsequent assessments.

- Tumor burden assessments will be performed based on modified RECIST 1.1 and iRECIST guidelines ([Appendix 11](#) and [Appendix 12](#)). To confirm disease progression, a second MRI/CT scan must be performed 4-6 weeks after the first detection of radiographical progression. If a subject continues AMG 256 treatment after confirmation of radiographic progression disease, CT/MRI assessment will be performed every 8 ($\pm$ 1) weeks thereafter.

⁹ All subjects must have MRI of the brain performed within [REDACTED] prior to the first dose of AMG 256. In subjects with known brain metastasis, brain MRI scans must be conducted at screening and at the same schedule as radiologic imaging and tumor assessments. Brain MRI can also be performed at any time if clinically indicated. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. The same contrast and modality used at screening should be used for all subsequent assessments.

¹⁰ All visible cutaneous and subcutaneous tumor lesions must be documented digitally using standardized photographic images including a ruler for scale as part of the image.

¹¹ Tumor markers, if applicable, are required at screening and every 8 ($\pm$ 1) weeks post-therapy initiation until clinically significant disease progression or deterioration, withdrawal of consent or start of new anticancer therapy.

¹² AMG 256 will be administered by intravenous infusion on [REDACTED] of every [REDACTED] cycle. AMG 256 should be administered on the scheduled day $\pm$ 1 day. See [Table 6-1](#) for infusion times.

¹⁷ Follow up visits will occur as follows:

- Safety follow up visits will occur 30 (+ 7) days and 90 ($\pm$ 7) days after the last dose of AMG 256.
- Long term follow-up (LTFU) phone call will be done 6 months ($\pm$ 1 week) after the last dose to collect information on start of new therapies, and disease status.

¹⁸

2. Introduction
2.1 Study Rationale
2.1.1 Overview

Extensive clinical experience has shown that the therapeutic effect of checkpoint inhibition, primarily with PD-1/PD-L1 but also with CTLA-4, is more closely associated with the inherent characteristics of the tumor (ie, mutational burden or dominant neoantigens) than with the tissue of tumor origin. This has led to the notion of “cold” and “hot” tumors depending on the tumor infiltration of reactive T cells. Therefore, the cancer community has been considering over the past several years different types of immunotherapy combinations with checkpoint blockade, including recombinant IL-21 (rIL-21), to enhance T cell infiltration and reactivity (reviewed in [Lewis 2017](#)).

PD-1 targeting while concomitantly delivering an IL-21 signal can lead to improved quantity and quality of T cell responses based on durable responses observed after ex-vivo priming with rIL-21 combined with CTLA-4 blockade in patients who had previously been resistant to this combination ([Chapuis et al, 2016](#)). This and several other studies reported below support the hypothesis that the simultaneous blockade of PD-1 and activation of IL-21 with a bifunctional fusion protein can lead to improved outcomes in cancer patients.

AMG 256 is a bifunctional fusion protein consisting of an anti-PD-1 blocking antibody fused to an IL-21 mutein. The IL-21 cytokine in the fusion protein has been mutated to diminish its affinity for IL-21R; this modification serves to reduce the stimulation of cells that express IL-21R. Co-expression of IL-21R and PD-1 enables the binding of the anti-PD-1 antibody portion of the fusion protein allowing for a more stable interaction between the IL-21 mutein domain and IL-21R which leads to the activation of the IL-21 pathway. In addition to serving as a means of directing AMG 256 to PD-1-expressing cells, thereby targeting IL-21 activation in PD-1 positive only cells, the anti-PD-1 antibody portion of the fusion protein blocks the interaction between PD-1 and ligands PD-L1/L2, thereby releasing the inhibitory signal that resulted from the interaction.

The combination of PD-1 blockade with IL-21 signaling at the T cell level is expected to:

- 1) Enhance T cell function in cancer.
- 2) Address limitations of either anti-PD-1s or rIL-21:
 - Efficacious in a number of different solid tumors, especially those with highest immunogenicity (ie, highest tumor mutational burden and neoantigen load)
 - Efficacious in subsets of patients, especially those with so-called “hot” tumors

- Efficacious for a limited period of time in patients developing innate (primary) or acquired (secondary) resistance to checkpoint blockade ([Jenkins et al, 2018](#))
- Systemic administration of recombinant IL-21 that activated both PD-1 positive and PD-1 negative immune cells improved anti-tumor immunity but also had dose-limiting toxicities due to its broad activation of (PD-1 negative) immune cells.
- Targeted IL-21 delivery (through PD-1) is expected to enable increased efficacy with potentially minimal additional toxicity beyond anti-PD1 monotherapy

The primary objective of this phase I study is to evaluate the safety, tolerability and estimated dosing of AMG 256 in adult subjects with advanced solid tumors. The secondary objectives are to evaluate the preliminary antitumor activity, pharmacokinetics and immunogenicity of AMG 256. Additionally, exploratory objectives are included to identify potential [REDACTED]

[REDACTED]
[REDACTED] and to evaluate ADA/immunogenicity.

2.1.2 PD-1 and PD-L1 Blockade In Cancer

Programmed death receptor 1 (PD-1) is an inhibitory receptor expressed on the surface of activated T cells normally involved with immune tolerance and preventing tissue damage associated with chronic inflammation. Interaction of PD-1 with its ligands, programmed death ligand 1 and 2 (PD-L1, also known as B7-H1 or CD274, and PD-L2, also known as B7-DC or CD273), dampens T-cell receptor signaling, leading to downregulation of T-cell activation, proliferation, and T-cell-mediated antitumor immune response. The PD-1 pathway represents one of the immune checkpoints used by tumors to suppress antitumor immunity.

Therapeutic blockade of PD-1 or PD-L1 with monoclonal antibodies (mAbs) leads to durable tumor regressions and overall survival benefits in patients with several cancer types. PD-1 is highly expressed on activated T and B cells and its ligands have been identified as PD-L1 and PD-L2. PD-L1 and PD-L2 have been shown to down-regulate T cell activation upon binding to PD-1. Blockade of PD-1 suppresses its negative signal and amplifies T cell responses and has elicited durable antitumor responses and long-term remissions in a subset of patients with a broad spectrum of cancers ([Lewis et al, 2017](#)).

Clinical responses to PD-1 blockade are associated with increased PD-L1 expression on tumor-resident cells, induced by preexisting tumor-infiltrating lymphocytes (TIL). Additionally, PD-1 blockade can expand intratumoral memory cells ([Ribas et al, 2016](#)).

The currently available anti-PD-1 antibodies that inhibit the interaction of PD-1 with PD-L1 and PD-L2 have been successfully used in a variety of cancer types. PD-1 blockade appears to provide a good balance of efficacy and toxicity of among many checkpoint blockade strategies tested to date.

2.1.3 Recombinant IL-21 in Cancer

IL-21, a member of the common gamma chain cytokine family, is produced by activated CD4+ T cells and natural killer (NK) T cells. CD4 T cells are the primary source of IL-21, which binds to a heterodimeric IL-21 receptor broadly expressed in the hematopoietic system (B & T cells and myeloid cells). IL-21 is a pleiotropic cytokine that regulates the activity of both innate and specific immunity. Indeed, it co-stimulates T and natural killer (NK) cell proliferation and function and regulates B cell survival and differentiation and the function of dendritic cells. IL-21 stimulates expansion and increases cytotoxicity of CD8+ T cells and enhances T cell-dependent B cell proliferation and antibody production. Treatment with recombinant human IL-21 (rIL-21) has been shown to produce antitumor activity in nonclinical and clinical studies. Pharmacokinetics (PK) of rIL-21 are dose-dependent, and its estimated terminal half-life is short, ranging between 1 and 4 hours in humans and cynomolgus monkeys. Pharmacodynamic analyses of rIL-21-treated patients indicate that rIL-21 can activate multiple cell types and immune response pathways. IL-21 cytokine has a dual role, immune suppression and immune potentiation ([Spolski et al, 2014](#), [Lewis et al, 2017](#)).

IL-21 shapes the immune response and is essential for preservation of memory T cells. T cells primed in vitro in the presence of IL-21 have characteristics of memory T cells, exhibiting enhanced persistence in vivo and providing superior tumor control ([Palmer et al, 2009](#)). Overexpression of IL-21 in transgenic mouse boosts CD8+ memory T cell expansion ([Allard et al, 2007](#)). In vitro studies have confirmed the role of IL-21 in enhancing the enrichment and expansion of memory stem T cells, with significant clinical implications for the generation of this memory T cell subset for adoptive cell therapy of patients with cancer ([Alvarez-Fernández et al, 2016](#)). Similarly, T cell therapy using IL-21–primed cytotoxic T cells combined with CTLA-4 blockade results in durable tumor regression ([Chapuis et al, 2016](#)).

The antitumor activity of IL-21 has been demonstrated in different tumor models, through mechanisms involving the activation of NK and T or B cell responses ([Lewis et al, 2017](#); [Spolski et al, 2014](#)). IL-21 exerts divergent effects on different lymphoid cell leukemia and lymphomas, as it may support cell proliferation or on the contrary induce growth

arrest or apoptosis of the neoplastic lymphoid cells (Croce et al, 2015). Moreover, IL-21's antitumor activity can be potentiated by its combination with other immune-enhancing molecules, such as mAbs recognizing tumor antigens, chemotherapy, or molecular targeted agents (Chapuis et al, 2016; Spolski et al, 2014). Clinical phase I-II studies of IL-21 in cancer patients showed immune stimulatory properties, manageable toxicity profile, and antitumor effects in a fraction of patients. As such, IL-21 is a suitable for combinational therapeutic regimens with other agents (Lewis et al, 2017; Spolski et al 2014; Thompson et al, 2008; Davis et al, 2009).

IL-21 or IL-21 gene transfer has been widely exploited in preclinical models of cancer immunotherapy either alone or in combination with cellular or molecularly defined vaccines, antibodies, other cytokines, or immune checkpoint blockers. These studies demonstrated that IL-21 triggers distinct mechanisms of antitumor immunity, leading to significant therapeutic effect and disclosed synergistic interactions with different molecules (Nakano et al, 2006; Di Carlo et al, 2004; Pan et al, 2013).

Based on these encouraging preclinical data, clinical trials of IL-21 as a single agent or in combination with other drugs were performed in different cancers, including metastatic melanoma, renal cell carcinoma, ovarian cancer, B cell lymphoma and acute myeloid lymphoma. Clinical phase I/II studies have shown that IL-21 has manageable toxicities and antitumor activity, leading to objective responses or disease stabilizations in a fraction of metastatic melanoma and renal cancer patients (Davis et al, 2007; Davis et al, 2009; Thompson et al, 2008; Schmidt et al, 2010; Hashmi et al, 2010; Croce et al, 2015). Although complete or partial responses have been rare in most reported studies (usually less than 10%), occasionally higher overall response rates have been observed. A phase 2 in metastatic melanoma reported ORR of 22.5% in patients with no systemic therapy who received intravenous bolus injection of IL-21 (Petrella et al, 2012). Despite relative low response rates overall, many patients across IL-21 studies were able to tolerate the treatment with stable disease. For example, in a phase 1 study of recombinant IL-21, among metastatic melanoma cohort (N= 24), one patient (4%) had a CR and 11 (45%) had SD. In the same study, among patients with RCC (N= 19), four patients (21%) had a PR and 13 (68%) had SD (Thompson et al, 2008).

2.1.4 Combination of PD-1/PD-L1 Inhibition and Recombinant IL-21 in Cancer

In view of its acceptable tolerability but low activity, rIL-21 is most likely suitable for combinational regimens of cancer immunotherapy. In fact, two clinical studies have addressed the possible cooperative effects of rIL-21 with immune checkpoint blockers:

- A phase I study of rIL-21 combined with the anti-CTLA4 mAb ipilimumab in unresectable stage III or stage IV melanoma (NCT01489059) and
- A safety study of rIL-21 with the anti-PD-1 mAb nivolumab in advanced or metastatic solid tumors (NCT01629758).

A recent study has shown that the combination of rIL-21 and checkpoint blockade facilitated the effector function of exhausted NK cells isolated from cancer patients. This effect was driven by the infiltration of NK cells into MHC class I-deficient tumors, suggesting that the efficacy of checkpoint blockade can be enhanced through the administration of rIL-21 for patients with advanced cancer displaying MHC class I-low/deficient tumors ([Seo et al, 2018](#)).

2.2 Background

2.2.1 Disease

As discussed earlier, therapeutic blockade of PD-1 or PD-L1 with monoclonal antibodies (mAbs) can lead to durable tumor response and overall survival benefits in many patients across several cancer types. However, a significant proportion of patients do not respond to these agents and there is little known about biomarkers predictive of benefit from checkpoint inhibitors. Therefore, a significant area of unmet need still exists. For instance, response rate to PD-1/ PD-L1 blockade in urothelial carcinoma is approximately 13-20% across five different agents ([Powles et al, 2018](#)). Similarly, among previously treated patients with NSCLC receiving a checkpoint inhibitor, overall response rates are approximately 20% across different PD-1 or PD-L1 inhibitors ([Herbst et al, 2016](#); [Brahmer et al, 2015](#); [Borghaei et al, 2015](#); [Rittmeyer et al, 2017](#)) and 27-39% PD-1 inhibitor, pembrolizumab, when used as a single agent frontline treatment prior to systemic chemotherapy ([Mok et al, 2019](#)).

Among many malignancies with an established role for PD-1/PD-L1, once patients progress after receiving checkpoint inhibitor treatment (PD-1/PD-L1, CTLA-4 inhibitor), their treatment options will be limited to chemotherapy with limited efficacy. (ex, melanoma, urothelial carcinoma).

In addition, in order to maximize efficacy among certain diseases, PD-1/ PD-L1 treatments get offered at earlier lines of therapy in combination with chemotherapy (ex, NSCLC, HNSCC), ([Gandhi et al, 2018](#); [Paz-Ares et al, 2018](#); [Rischin et al, 2019](#)). This approach, although leading to improved efficacy and survival among many patients, increases the overall toxicities of the treatment regimen and leaves fewer treatment options for patients beyond progression on first line systemic therapy such as single agent chemotherapy.

This study will enroll adult subjects (≥ 18 years old) with histologically or cytologically proven metastatic or locally advanced solid tumors, for which no standard therapy exists, standard therapy has failed, standard therapy is not available, or in the investigator's opinion standard therapy does not result in meaningful clinical response.

Dose escalation will be conducted in checkpoint inhibitor-naïve subjects; and dose expansion will be conducted in checkpoint inhibitor-exposed subjects with specific tumor types.

The specific tumor types in the expansion cohort will include NSCLC, melanoma, renal cell carcinoma, squamous cell carcinoma of the head and neck or skin and selected other diseases after failure of PD-1/PD-L1 treatments. These tumor types have been selected based on published response to PD-1/PD-L1 blockade and/or response to systemic rIL-21 therapy ([Hashmi et al, 2010](#); [Croce et al, 2015](#)).

2.2.2 Amgen Investigational Product Background: AMG 256

AMG 256 is a bifunctional fusion protein consisting of an anti-PD-1 blocking antibody fused to an IL-21 mutein. The IL-21 cytokine in the fusion protein has been mutated to diminish its affinity for IL-21R; this modification serves to reduce the stimulation of cells that express IL-21R. Co-expression of IL-21R and PD-1 enables the binding of the anti-PD-1 antibody portion of the fusion protein allowing for a more stable interaction between the IL-21 mutein domain and IL-21R which leads to the activation of the IL-21 pathway. In addition to serving as a means of directing AMG 256 to PD-1-expressing cells, the anti-PD-1 antibody portion of the fusion protein blocks the interaction between PD-1 and ligands PD-L1/L2, thereby releasing the inhibitory signal that resulted from the interaction.

Refer to the [Investigator's Brochure](#) for further data on AMG 256.

2.2.2.1 Nonclinical Pharmacology

In vitro pharmacology:

AMG 256 is a fully human bifunctional fusion protein, consisting of a bivalent PD-1 antibody fused to a monomeric IL-21 mutein. The anti-PD-1 antibody domain of the fusion protein binds to human and cynomolgus monkey PD-1 with high affinity and blocks the ability of these receptors to interact with ligands, PD-L1 and PD-L2. The ligand blocking activity of AMG 256 was evaluated in multiple in vitro assays (cell based and recombinant ligands) and the expected dose-dependent activity was observed, indicating that AMG 256 is a potent inhibitor of human and cynomolgus monkey PD-1 binding to human ligands.



The ability of AMG 256 to stimulate IL-21R in PD-1-expressing cells is the result of the anti-PD-1 binding domain of AMG 256 binding to PD-1 and stabilizing the interaction between the IL-21 mutein and IL-21R.

In vivo pharmacology:

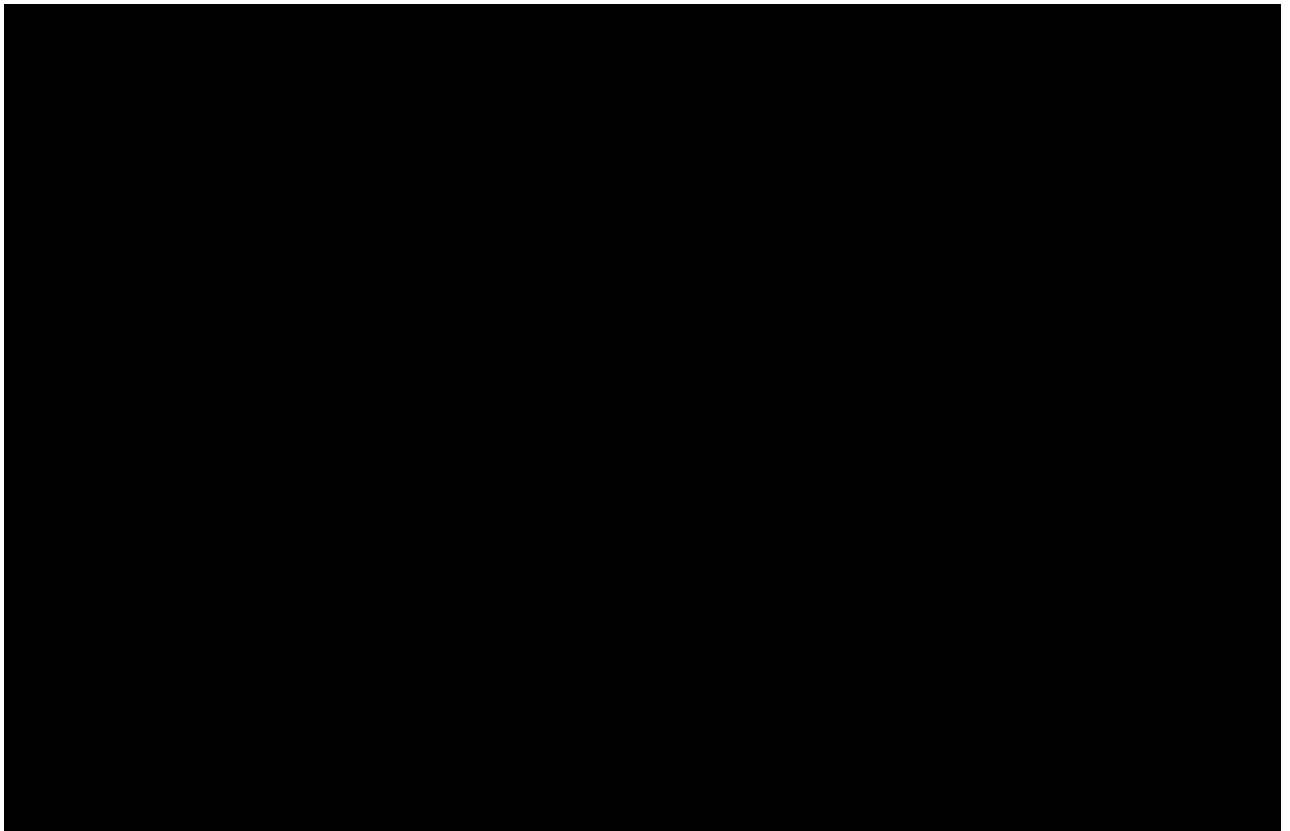
The in vivo activity of an AMG 256 surrogate was evaluated in a CMV-SK-MEL-30-Luc-Hi xenograft model where CMV-specific human T cells were adoptively transferred into immunocompromised mice bearing CMV antigen-expressing tumor cells. 



 These data demonstrate that the IL-21 mutein enhanced the anti-tumor activity of an anti-PD-1 antibody in this model.

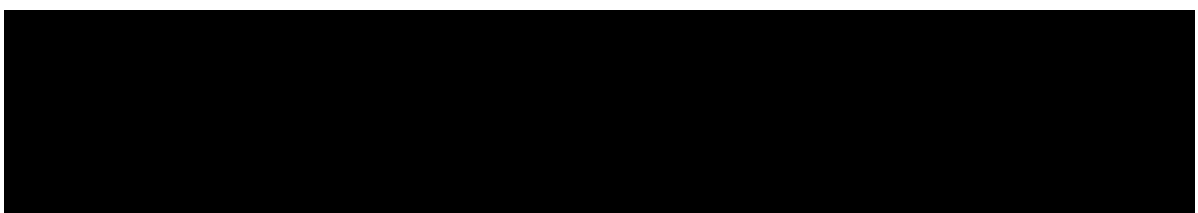
The in vivo activity of AMG 256 was further evaluated in cynomolgus monkeys following repeat dose IV administration of doses ranging from [REDACTED] to [REDACTED] mg/kg. Target coverage, as reflected by PD-1 receptor occupancy, was achieved following the first dose of AMG 256. AMG 256 administration induced transient declines in lymphocytes, consistent with reported effects of IL-21 cytokine and anti-PD-1 antibodies in clinical trials ([Thompson et al, 2008](#); [Brahmer et al, 2010](#)). Transient increases in STAT3 phosphorylation were also observed.

2.2.2.2 Nonclinical Pharmacokinetics



2.2.2.3 Nonclinical Toxicology

Nonclinical safety information about AMG 256 was derived from two exploratory repeat dose studies and a GLP repeat dose toxicology study in cynomolgus monkeys and an in vitro assessment of cytokine release. Observations in the cynomolgus monkey were consistent with various factors, including interactions with the targets of AMG 256 (ie, PD-1 and IL-21R) and its immunogenicity profile.



[REDACTED]

AMG 256-related observations were also as expected based on the generally consistent effects of rhIL-21 administration to cynomolgus monkeys or humans including acute phase responses, anemia, lymphopenia, and transient hepatic enzyme elevations (Davis et al, 2007; Davis et al, 2009; Grünwald et al, 2011; Thompson et al, 2008; Timmerman et al, 2012; Waggle et al, 2012). [REDACTED]

[REDACTED]

AMG 256-related observations were also consistent with the spectrum of immunogenicity-related responses to the administration of biotherapeutics in cynomolgus monkeys. [REDACTED]

[REDACTED]

[REDACTED]. Together, these data were indicative of an immunogenicity-related response and are broadly consistent with published case studies.

[REDACTED]

An in vitro assay validated for the evaluation of acute cytokine release risk was conducted using resting human T cells. AMG 256 did not induce cytokine release above background levels under the assay conditions tested. In contrast, transient cytokine elevations were observed following administration of AMG 256 in the cynomolgus monkey studies. The explanation for the discrepancy in results between the in vitro and in vivo studies is not clear but may be related to differences in the expression of PD-1 and/or IL-21R on cells that are the target(s) of AMG 256 in the human in vitro system and in vivo in the cynomolgus monkey.

2.3 Benefit/Risk Assessment

This is a first-in-human study with AMG 256. Data from nonclinical toxicity studies of AMG 256 suggests that the overall benefit/risk profile favors clinical development of AMG 256 for patients with advanced solid tumors. Clinical signs and symptoms, along with other safety laboratory parameters, will be monitored during the study and at the appropriate time points to ensure subjects' safety.

Refer to the [Investigator's Brochure](#) for further data on AMG 256.

Table 2-1. Key Safety Risks for AMG 256

Safety Risk	Description
Immunogenicity	Anti-drug antibodies (ADAs) of the IgG and IgE isotypes were identified in cynomolgus monkeys administered AMG 256. The development of ADAs in subjects administered AMG 256 may lead to hypersensitivity and coagulopathies (see below).
Infusion-Related / Hypersensitivity Reactions	Clinical signs and symptoms of hypersensitivity-type reactions were observed in some cynomolgus monkeys. Subjects administered AMG 256 should be closely monitored for signs and symptoms suggestive of infusion-related and hypersensitivity reactions, including anaphylaxis. Signs and symptoms may include pyrexia, chills, rigors, flushing, urticaria, hypotension, dyspnea, wheezing, headache, back pain, and abdominal pain, which may be severe or life-threatening.

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Table 2-1. Key Safety Risks for AMG 256

Safety Risk	Description
Coagulopathy (including disseminated intravascular coagulation [DIC])	Systemic coagulopathy attributed to ADA-mediated immune complex disease was observed in cynomolgus monkey studies. Subjects administered AMG 256 should be closely monitored for signs and symptoms suggestive of disseminated intravascular coagulation (DIC), such as onset of high fever, hypotension, shortness of breath, confusion, severe malaise, ecchymoses, purpura, petechiae, and bleeding including at mucosal membranes. Complications of DIC can include organ failure and may be life-threatening or fatal.
Immune-Related (Inflammatory) Adverse Events	Anti-PD-(L)1 therapies have been associated with a spectrum of inflammatory effects related to the mechanism of action. These immune-related adverse events can occur in any organ system or tissue and include toxicities such as pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin reactions, encephalitis, and other immune-related adverse reactions.
Cytopenias	In cynomolgus monkey studies, AMG 256-related changes in hematologic parameters included transient decreases in red cell mass, platelets, and white blood cell count. Transient cytopenias have also been observed in clinical studies of rhIL-21.
Embryofetal Toxicity	Blockade of PD-L1 signaling has been shown in animal models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, there is the possibility of fetal harm if AMG 256 is administered during pregnancy.

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3. Objectives and Endpoints

Objectives	Endpoints
Secondary	
To evaluate the pharmacokinetics (PK) of AMG 256	PK parameters of AMG 256 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 the preliminary antitumor activity of AMG 256	- Objective Response (OR) per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and iRECIST - Duration of Response (DOR) - Progression-free survival (PFS), 6-month and 1-year PS - Disease Control Rate (DCR) - Duration of stable disease - Overall Survival (OS), 1 and 2-year
To assess the immunogenicity of AMG 256	Subject incidence of anti-AMG 256 antibodies

Objectives	Endpoints
Exploratory	

4. Study Design

4.1 Overall Design

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study to evaluate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AMG 256 in subjects with advanced solid tumors. AMG 256 will be administered by intravenous (IV) infusion on [REDACTED] cycle or [REDACTED] and [REDACTED] of every [REDACTED] cycle. The study may be conducted in Australia, Belgium, United Kingdom, United States, Poland, Japan and China. Other countries or regions may participate. The study will be conducted in 2 parts: Part 1 – Dose Escalation and Part 2 – Dose Expansion. Part 1 is intended to evaluate the safety, tolerability, PK, and PD of AMG 256 and determine the maximum tolerated dose (MTD) in subjects with advanced solid tumors using a Bayesian Logistics Regression Model (BLRM) design. Part 2 will further evaluate the safety of the MTD and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) in specific tumor types. The dose expansion part of the study (Part 2) can be opened once the MTD/RP2D has been determined in Part 1. The dose escalation part of the study will consist of approximately 40 subjects and the dose expansion will consist of approximately 60 additional subjects. Dose escalation will be conducted in checkpoint inhibitor-naïve subjects; and dose expansion will be conducted in checkpoint inhibitor-exposed subjects with specific tumor types. The DLT evaluation period will be 28 days. Based on emerging clinical efficacy data, the cancer types explored in the expansion part may be modified. Administration of AMG 256 (in part 1 and part 2) may continue until evidence of disease progression, intolerance to study medication, withdrawal of consent, or in the absence of the above up to 12 months if a subject achieves a complete response, and up to 24 months if partial response or stable disease is achieved.

Dose Escalation – Part 1

Dose escalation cohorts will estimate the safety, tolerability, PK, and PD of different doses of AMG 256 in subjects with advanced solid tumors who have not received treatment previously with a checkpoint inhibitor. Subjects will receive AMG 256 [REDACTED] or [REDACTED]. Dose escalation will begin with [REDACTED] dosing and [REDACTED] dosing will begin as indicated in the Study Schema (Figure 1-1). The [REDACTED] dosing may be initiated at lower doses or later than indicated, based on emerging safety, PK and/or preliminary response data. Dose escalation will begin with single subject cohorts treated at the lowest planned dose level of [REDACTED] mg. The cohort size will be increased to N = 2-4 subjects after observation of treatment-related adverse events of grade 2 or higher; or escalation has reached the presumed efficacious dose; or is recommended by the dose level review team (DLRT) to further evaluate a cohort.

To minimize the number of subjects treated at potentially toxic dose levels, subjects in each multiple subject cohort will be enrolled sequentially (Section 11.10).

- During dose escalation, [REDACTED] subjects will be sequentially enrolled with a minimum of [REDACTED] between the first and second subjects being dosed within a cohort; and a minimum of 1 day between the second, third and fourth subjects within a cohort.
- During dose escalation, [REDACTED], subjects will be sequentially enrolled with a minimum of [REDACTED] between the first and second being dosed within a cohort; and a minimum of 1 day between the second, third and fourth subjects within a cohort.

The sequential dosing of subjects within a cohort should be maintained as best possible for the [REDACTED] of treatment to minimize the potential for multiple subjects experiencing hypersensitivity reactions on the same day. The goal of the sequential dosing is to avoid multiple subjects receiving the same dose number on the same day during the first two cycles (ie, two subjects receiving cycle 1, [REDACTED] dose on the same day).

Dose escalation will follow the planned Study Schema schedule. If no DLT is observed, dose escalation will continue to the next planned dose cohort as per the Study Schema. 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 DLRT using the dose level recommendation from the BLRM, as appropriate, and by evaluating all available safety data, including late onset immune-mediated toxicities, laboratory data, and PK information.

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

- The subject has not experienced any clinically significant $\geq$ grade 2 adverse events (deemed treatment related by the investigator) during treatment

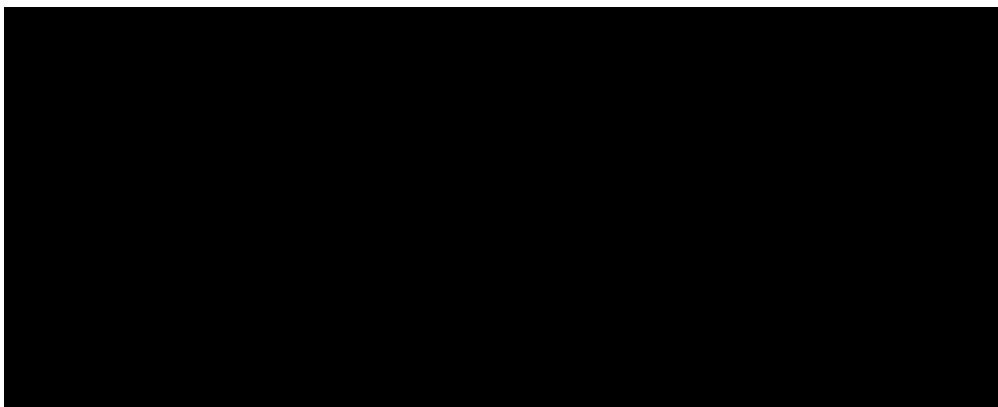
Subjects who do not proceed to a higher dose may continue to receive additional cycles at the original dose. Dose escalation will continue until any of the following events:

- 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 10) 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 used, to better estimate the RP2D and better characterize the safety, efficacy and pharmacodynamics of AMG 256 and may be concurrent with dose escalation to identify the MTD.

Dose Expansion – Part 2

Upon completing the dose escalation part of the study and depending on data obtained, dose expansion may proceed. The RP2D/MTD will be administered in the dose expansion. Dose expansion will open to 2 groups with certain advanced solid tumors that are checkpoint-inhibitor exposed, as indicated below. The first 6 subjects enrolled during expansion will be enrolled sequentially, with a minimum of [REDACTED] between the subjects initiating treatment.



Dose expansion in all groups may be done concurrently.

The overall study design is described by a study schema in [Section 1.2](#). The endpoints are defined in [Section 3](#).

4.2 Number of Subjects

Approximately 100 subjects with advanced solid tumors will be enrolled in the study. Up to 40 evaluable subjects will be enrolled in dose escalation and up to 60 evaluable subjects will be enrolled in dose expansion.

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

4.2.1 Replacement of Subjects

Subjects that are not DLT-evaluable may be replaced. DLT-evaluable is defined as:

- Subject who has received at least 90% of the planned dose of investigational product and is followed for at least 28 days, or
- Subject who has experienced a DLT.

4.2.2 Number of Sites

Approximately 18 investigative sites in Australia, Belgium, United Kingdom, United States, Poland, Japan and China may be included in the study. Other countries or regions may participate. Sites that do not enroll subjects within 3 months (provided slots are available) of site activation may be closed.

4.3 Justification for Investigational Product Dose

The PK of AMG 256 in humans was estimated using allometric scaling of PK parameters obtained from nonclinical studies in cynomolgus monkeys.

The proposed doses of AMG 256 for the FIH study are [REDACTED] and [REDACTED] mg [REDACTED] and [REDACTED] and [REDACTED] mg [REDACTED] as short-term IV infusions [REDACTED]

[REDACTED]
[REDACTED]) in subjects with advanced solid tumors.

The AMG 256 starting dose was based on the [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]



Furthermore, relative to the use of 1/6th of the highest non-severely toxic dose (HNSTD) of [REDACTED] mg/kg in cynomolgus monkeys as the basis for defining the starting dose for anti-cancer drugs (ICH S9, 2009), a [REDACTED] mg dose remains a more conservative approach. This approach is also supported by the calculation of the expected human exposure multiples, which were approximately [REDACTED] and [REDACTED]-fold for AUC and C_{max}, respectively, at a starting dose of [REDACTED] mg relative to the HNSTD of [REDACTED] mg/kg.

The highest planned human [REDACTED] dose is [REDACTED] mg; the predicted exposure multiples for AUC and C_{max} at this dose are calculated to be [REDACTED]- and [REDACTED]-fold, respectively, when compared to the AUC and C_{max} at the HNSTD in monkeys. The highest planned human [REDACTED] dose is [REDACTED] mg; the predicted exposure multiples for AUC and C_{max} at this dose are calculated to be [REDACTED] and [REDACTED]-fold, respectively, when compared to the AUC and C_{max} at the HNSTD in monkeys. Dosing schedule and dose escalation decisions will be guided primarily by the safety and tolerability of AMG 256.

Efficacious doses of AMG 256 were predicted based on results of in vitro pharmacological activity studies on AMG 256-mediated blockade of PD-1 binding to PD-L1 in two cell-based systems and STAT3 phosphorylation (downstream of IL21 receptor activation) in PD-1 positive cells. Early signs of efficacy in subjects are predicted to be observed following [REDACTED] administration of approximately [REDACTED] mg AMG 256 or following [REDACTED] administration of approximately [REDACTED] mg AMG 256 based on trough coverage of the concentrations of 90% of maximal effect (EC₉₀) and of maximal inhibitory effect (IC₉₀) of AMG 256 pharmacological activities in vitro (assuming [REDACTED] of the serum exposure in the tumor).

The study will begin with a [REDACTED] dosing schedule. A [REDACTED] dosing schedule may be initiated in later cohorts based on emerging safety and tolerability data; the planned

initial [REDACTED] dose is [REDACTED] mg [REDACTED] which is expected to be in the efficacious dose range. [REDACTED] dosing may be initiated at doses lower than [REDACTED] mg [REDACTED] based on emerging safety, PK and/or preliminary response data from FIH study that supports anti-tumor activity with lower [REDACTED] doses.

4.4 End of Study

4.4.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

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, additional antibody testing), as applicable.

4.4.2 Study Duration for Subjects

It is anticipated that an individual subject will participate in the study for up to approximately 2.5 years. This includes, the screening period lasting up to 28 days, a treatment period up to 2 years, and a follow up period of 6 months after end of treatment.

The actual duration for individual subjects will vary depending upon tolerability of AMG 256, evidence of clinical and radiologic progression, and willingness to participate in the study.

4.5 Patient Input on Study Design

Patient input was not obtained for the design of this study.

5. Study Population

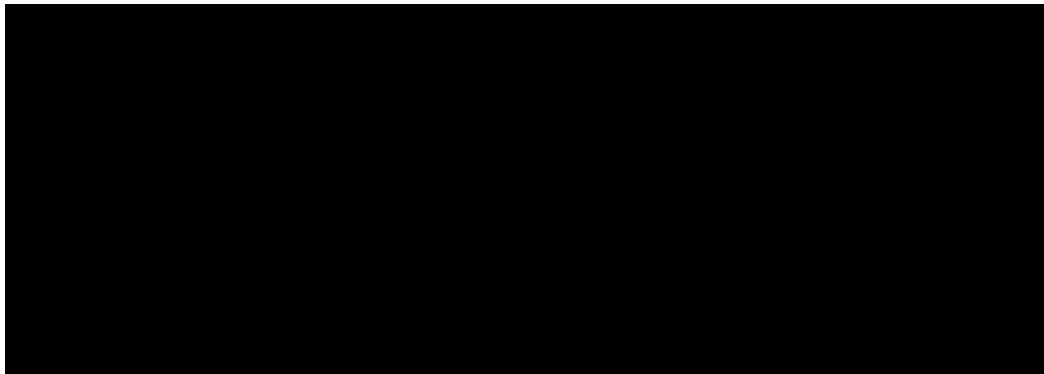
Eligibility criteria will be evaluated during screening. Subjects must meet eligibility criteria on Cycle 1, [REDACTED] of treatment.

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

5.1 Inclusion Criteria

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

- 101 Subject has provided informed consent prior to initiation of any study specific activities/procedures.
- 102 Age $\geq$ 18 years at the time of signing informed consent.
- 103 Life expectancy of > 3 months, in the opinion of the investigator.
- 104 Subject must have histologically or cytologically proven metastatic or locally advanced solid tumors not amenable to curative treatment with surgery or radiation for which:
- No standard therapy exists, or
 - Standard therapy has failed, not available, or
 - In the investigator's opinion, standard therapy does not result in meaningful clinical benefit.



- 105 **Dose Expansion:** Subject must have previously been treated with an anti-programmed death 1 (PD-1), anti-PD-L1, and/or CTLA-4.
- 106 At least 1 measurable lesion ≥ 10 mm which has not undergone biopsy within 3 months of screening scan. This lesion cannot be biopsied at any time during the study.
- 107 **Cohorts 6-9, 1a and 2a in escalation and expansion:** Subjects must have a readily tumor lesion for biopsy and be willing to undergo biopsies during screening (an archival tumor sample may be acceptable if obtained within 6 months of enrollment and subject has not received any other treatment since sample was obtained) and during treatment with AMG 256.
- 108 Subjects with treated brain metastases are eligible provided they meet the following criteria:
- Definitive therapy was completed at least 2 weeks prior to enrollment.

- No evidence of radiographic CNS progression or CNS disease following definitive therapy and by the time of study screening. Patients manifesting progression in lesions previously treated with stereotactic radiosurgery may still be eligible if pseudoprogression can be demonstrated by appropriate means and after discussion with the medical monitor.
- Any CNS disease is asymptomatic, any neurologic symptoms due to CNS disease have returned to baseline or are deemed irreversible, the patient is off steroids for at least 7 days (physiologic doses of steroids are permitted), and the patient is off or on stable doses of anti-epileptic drugs for malignant CNS disease.

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

110 Hematologic function, as follows (transfusions or growth factor support must not be administered within 7 days prior to obtaining screening labs):

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
- Platelet count $\geq 75 \times 10^9/L$
- Hemoglobin ≥ 9 g/dL

111 Adequate renal laboratory assessments, as follows:

Dose Escalation: Estimated glomerular filtration rate based on MDRD (Modification of Diet in Renal Disease) calculation ≥ 60 ml/min/1.73 m²

Dose Expansion: Estimated glomerular filtration rate based on MDRD (Modification of Diet in Renal Disease) calculation ≥ 45 ml/min/1.73 m²

112 Hepatic function, as follows:

- Total bilirubin $\leq 1.5 \times$ ULN or $\leq 3 \times$ ULN for subjects with liver metastasis
- AST $\leq 3 \times$ ULN or $\leq 5 \times$ ULN for subjects with liver metastasis
- ALT $\leq 3 \times$ ULN or $\leq 5 \times$ ULN for subjects with liver metastasis
- Alkaline phosphatase $\leq 2.5 \times$ ULN or $\leq 5 \times$ ULN for subjects with liver metastasis

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5.2 Exclusion Criteria

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

Disease Related

- 201 Primary brain tumor, untreated or symptomatic brain metastases and leptomeningeal disease.

Other Medical Conditions

- 202 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 noninvasive carcinoma or carcinoma in situ.
- 203 History of solid organ transplantation.
- 204 Major surgery within 28 days of study day 1.

Prior/Concomitant Therapy

- 205 Anti-tumor therapy (radiotherapy, chemotherapy, antibody therapy, molecular targeted therapy, oncolytic therapy) within 21 days prior to study day 1 or investigational agent within 28 days prior to study day 1.
Note: Palliative radiotherapy is permitted.
- 206 **Dose Escalation:** Prior treatment with anti-programmed death 1 (PD-1), anti-PD-L1, CTLA-4, or other checkpoint inhibitor drugs.
- 207 **Dose Expansion:** Treatment with anti-programmed death 1 (PD-1), anti-PD-L1, and/or CTLA-4 within 4 weeks prior to study day 1.
- 208 **Dose Expansion:** More than 2 lines of prior immunotherapy. Prior immunotherapy limited to PD-(L)1 inhibitor and/or CTLA 4 inhibitor. One line of prior oncolytic therapy is permitted.

- 209 Live vaccine therapy within 4 weeks prior to study day 1.
- 210 Current treatment with immunosuppressive corticosteroid defined as > 10 mg prednisone daily or equivalent. Corticosteroids with no or minimal systemic effect (such as topical or inhalation) are permitted.

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

- 212 Evidence of active or radiological sequelae of non-infectious pneumonitis.
- 213 History of any immune-related colitis. Infectious Colitis is allowed if evidence of adequate treatment and clinical recovery exists and at least 3 months interval observed since diagnosis of colitis.
- 214 Positive/Non-negative results for Human Immunodeficiency Virus (HIV).
- 215 Hepatitis B and C based on the following results:
- Positive for hepatitis B surface antigen (HBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B)
 - Negative HBsAG and positive for hepatitis B core antibody: Hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B
 - Positive Hepatitis C virus antibody (HCVAb): hepatitis C virus RNA by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C
- 216 Active infection requiring oral or intravenous therapy.
- 217 Active or history of any autoimmune disease or immunodeficiencies. Subjects with diabetes Type 1, vitiligo, psoriasis, hypo- or hyper-thyroid disease not requiring immunosuppressive treatment are permitted.
- 218 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.
- 219 Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade 1, or are stable and well controlled with minimal, local, or

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non-invasive intervention AND there is agreement to allow by both the investigator and the Amgen Medical Monitor.

- 220 **Dose Expansion:** Any history of grade 3 or higher colitis, pneumonitis, or neurological toxicity OR unresolved toxicities from prior checkpoint inhibitor therapy, defined as not having resolved to CTCAE v5 grade 1.
Exception: hypothyroid status that is managed by levothyroxine

Other Exclusions

- 221 History of severe allergic reactions or severe acute hypersensitivity reaction.
- 222 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 3 months after the last dose of AMG 256.
- 223 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 3 months after the last dose of AMG 256. Refer to [Section 11.6](#) for additional contraceptive information.
- 224 Female subjects of childbearing potential with a positive pregnancy test assessed within 48 hours prior to day 1 of treatment by a serum pregnancy test.
- 225 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 5 months after the last dose of AMG 256. Refer to [Section 11.6](#) for additional contraceptive information.
- 226 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional 5 months after the last dose of AMG 256.
- 227 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 5 months after the last dose of AMG 256.
- 228 Subject has known sensitivity to any of the products or components to be administered during dosing.
- 229 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.
- 230 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

5.3 Subject Enrollment

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

The subject must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (beginning from time of consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The unique subject identification number will consist of 11 digits. The first 3 digits will represent the last 3 digits of the protocol number (ie, 144). The next 5 digits will represent the country code and site number (eg, 26001) and will be identical for all subjects at a particular site. The next 3 digits will be assigned in sequential order as subjects are screened (eg, 001, 002, or 003). For example, the first subject to enter screening at a site 26001 will receive the number 14426001001, and the second subject at the same site will receive the number 14426001002.

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

5.4 Screen Failures

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

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

6. Treatments

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

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

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 256 shown in [Table 6-1](#) below.

6.1 Treatment(s) Administered

6.1.1 Investigational Products

Table 6-1. Study Treatments

Study Treatment Name	Amgen Investigational Product: ^a AMG 256
Dosage Formulation	■ mg/mL solution for infusion
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Doses and infusion schedules will vary across treatment cohorts. For more information, refer to Study Schema Figure 1-1 . AMG 256 will be administered either on ■ cycle or ■ of every ■ cycle. AMG 256 should be administered on the scheduled day ±1 day.
Route of Administration	AMG 256 solution for infusion will be prepared for IV infusion and delivered through infusion lines using a syringe pump (Cohorts 1-3) and a preprogrammed infusion pump (Cohorts 4 and higher) approved for use in the country in which the subject is undergoing treatment.
Accountability	The quantity administered, start date/time, stop date/time, lot number of investigational product is to be recorded on each subject's CRF.

Footnotes defined on last page of the table

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Table 6-1. Study Treatments

Study Treatment Name	Amgen Investigational Product: ^a AMG 256
Dosing Instructions	<u>During Dose Escalation:</u> AMG 256 will be administered over [REDACTED] during cycles 1 and 2; [REDACTED] during cycle 3; [REDACTED] during cycle 4 and all subsequent cycles. Observation period will be a minimum of: [REDACTED] after each infusion during cycles 1 and 2; [REDACTED] after each infusion during cycle 3 and all subsequent cycles. For multi-subject cohorts in dose escalation, sites must receive written confirmation from the study team prior to all doses during cycles 1 and 2 with approval that it is safe to proceed with dosing. During cycles 1 and 2 for multi-subject cohorts in dose escalation, sites must notify the study team when a subject has been dosed and if subject experienced any significant adverse reaction (ie, infusion-related reaction or hypersensitivity reaction). Each participating site should avoid treating more than one subject on the same day during cycles 1 and 2. <u>During Dose Expansion:</u> For the first 3 subjects enrolled, AMG 256 will be administered over [REDACTED] during cycle 1; [REDACTED] during cycle 2; and [REDACTED] during cycle 3 and all subsequent cycles. For all remaining subjects enrolled, AMG 256 will be administered over [REDACTED]. The first 6 subjects enrolled will be observed for a minimum of: [REDACTED] after each infusion during cycle 1; [REDACTED] after each infusion during cycle 2; [REDACTED] after each infusion during cycle 3 and all subsequent cycles. All remaining subjects enrolled will be observed for [REDACTED] after each infusion beginning with cycle 1. <u>All subjects in dose escalation and dose expansion:</u> At time of discharge, subjects should be instructed to report any delayed reactions or signs of bleeding to the investigator immediately. Subjects are to be given the Symptoms Review Questionnaire (Appendix 13) with instructions to review the questions listed frequently and notify the investigator immediately if any changes are noticed. It is recommended the subjects be contacted between doses during cycles 1 and 2, to ensure compliance of monitoring symptoms presented in the questionnaire.

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^a AMG 256 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

To minimize the number of subjects treated at potentially toxic dose levels, subjects in each multiple subject cohort during escalation will be enrolled sequentially (Section 11.10). During dose escalation, [REDACTED] dosing subjects will be sequentially enrolled with a minimum of [REDACTED] between the first and second subjects within a cohort; and a minimum of 1 day between the second, third, and fourth subjects within a cohort. During dose escalation, [REDACTED] dosing subjects will be sequentially enrolled with a minimum of [REDACTED] between the first and second subjects within a cohort; and a minimum of 1 day between the second, third, and fourth subjects within a cohort. During expansion, the first 6 subjects enrolled will be enrolled sequentially, with a minimum of [REDACTED] between the subjects initiating treatment. The sequential dosing of subjects within a cohort should be maintained as best possible for the [REDACTED] of treatment to minimize the potential for multiple subjects experiencing hypersensitivity reactions on the same day. The goal of the sequential dosing is to avoid multiple subjects receiving the same dose number on the same day during the first two cycles (ie, two subjects receiving cycle 1, [REDACTED] dose on the same day).

The medical staff must closely observe patients for signs of anaphylaxis or any other potential adverse events. Subjects will be observed as indicated in Table 6-1.

Vital signs (blood pressure, heart rate, respiratory rate, pulse ox and temperature) should be checked and recorded as per the Schedule of Activities (Section 1.3).

Subjects should be treated and observed in an area with resuscitation equipment and other agents (epinephrine, intravenous corticosteroids, etc.) available. A nurse must be present in the immediate treatment area throughout the infusion and observation period. A physician must be in close proximity to the patient treatment area. In the event that a patient experiences an allergic/hypersensitivity reaction, see Table 11-3 for instructions on proper management. Patients should be instructed to report any delayed reactions to the investigator immediately.

6.1.2 Non-investigational Products

This study will not use non-investigational products.

6.1.3 Medical Devices

No investigational medical device(s) will be used in this study.

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

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

6.1.4 Other Protocol-required Therapies

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

6.1.5 Other Treatment Procedures

There are no other treatment procedures in this study.

6.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(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 investigational product provisioned and/or repackaged/modified by Amgen. AMG 256 is the investigational product in this study.

Amgen Rave EDC system is being used to report product complaints.

Regardless of the reporting method, all product complaints must be reported to Amgen within 24 hours of discovery.

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

Any anti-tumor therapy other than the investigational product, including cytotoxic and/or cytostatic drugs, hormonal therapy, systemic corticosteroids (except for subjects who were receiving ≤ 10 mg prednisone or equivalent at the time of enrollment are permitted to remain on it), immunotherapy or any biological response modifiers, any other investigational agent, and other immunosuppressive therapies are excluded.

Primary prophylactic use of hematopoietic growth factors such as granulocyte-colony stimulating factor (G-CSF) is not allowed during the DLT- evaluation period.

Administration of systemic corticosteroids, immunomodulators, and hormonal replacement therapy for the management of toxicities (eg, immune-related adverse events) is allowed; however, AMG 256 must be discontinued if ≥ 10 mg per day

prednisone or equivalent is continued for more than 12 weeks. Corticosteroids with no or minimal systemic effect (eg, topical, inhalation) are allowed.

Any live vaccine therapies for the prevention of infectious disease are not allowed (except administration of the inactive influenza vaccine).

Radiotherapy is not permitted except for palliation of symptoms and should be discussed with the sponsor's Medical Monitor first. Investigators should ensure that the need for radiation does not indicate progressive disease and that for subjects with measurable disease, radiation is not to the sole site of measurable disease.

The following procedures should also not be undertaken within the timeframes specified prior to enrollment and during the study:

- Participation in any investigational study (drug or device) within 28 days of study day 1
- Major surgery within 28 days of study day 1
- Enrollment into another investigational drug or device study

6.2 Dose Modification

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

Dose Level Determination

A recommendation to escalate to a higher dose cohort will only occur when the previous dose level has been found to be reasonably tolerated based on available study data through study day 28 of cycle 1 for all evaluable subjects and upon unanimous agreement of the DLRT members. Available data from previous cohorts will also be considered. Dose level recommendations will be made on a treatment cohort basis (not on an individual basis). After receiving the DLRT recommendation, Amgen will render a final decision and will issue a written notification of the dose change decision to investigators. Further information on dose level review meetings is provided in [Appendix 3 \(Section 11.3\)](#).

Dose Cohort Stopping Rules

The DLRT will 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. All available study data including demographics, medical history, concomitant medications, AEs, late onset immune-mediated toxicities,

electrocardiograms (ECGs), vital signs, laboratory results, and emerging PK or PD data will be reviewed.

The Amgen Medical Monitor may suspend dosing and convene a dose level review meeting (DLRM) at any time based on emerging safety data.

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

The DLT window (ie, DLT-evaluable period) will be the first [REDACTED] of AMG 256 treatment (starting cycle 1, day 1). The DLT window may also be extended to assess events starting within the window in case the DLT definition is time dependent.

The subject will be DLT evaluable if the subject has completed the DLT window as described above or experienced a DLT any time during the DLT window. A subject will not be DLT evaluable if he/she drops out before completion of the DLT-evaluable period for reasons other than a DLT. All available safety data for subjects who are not DLT-evaluable will still be evaluated and considered in DLRT recommendations (see also [Section 11.3](#)).

See [Section 4.2.1](#) for description of replacement of subjects.

An adverse event will be considered related to study treatment (possibly, probably, or definitely related to the study treatment) if there is a suspected “reasonable causal relationship” to the study treatment (ICH E2A), and not only a lack of an alternative explanation for the toxicity. All toxicities will be graded using the CTCAE version 5.0. The occurrence of any of the following toxicities during the DLT evaluation period (ie, [REDACTED] period from the initial administration of AMG 256) will be considered a DLT unless the toxicity is clearly and incontrovertibly due to disease progression or other extraneous causes:

- Any treatment related grade 5 toxicity
- Grade 4 neutropenia or thrombocytopenia > 7 days in duration
- Febrile neutropenia
- Grade 4 anemia
- Grade 3 or 4 non-hematologic toxicity, with the following exceptions:
 - DLT Exemption: Grade 3 endocrinopathies if manageable with replacement therapy
 - DLT Exemption: Grade 3 nausea/vomiting or diarrhea < 72 hours in the absence of maximal medical therapy
 - DLT Exemption: Grade 3 fatigue < 1 week

- DLT Exemption: Asymptomatic $\geq$ grade 3 electrolyte abnormalities that last < 72 hours, is not clinically complicated, and resolved spontaneously or responds to conventional medical interventions
- DLT Exemption: $\geq$ Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
- DLT Exemption: Other laboratory parameters of ≥ 3 , not considered clinically relevant, and improved to grade ≤ 2 within 72 hours.
- Recurrent grade 2 pneumonitis
- Delay in cycle 2 treatment for > 14 days due to an adverse event in the dose escalation portion of the study due to study drug-related toxicity
- Any other toxicity requiring permanent discontinuation of AMG 256 per [Appendix 4](#)

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

The cumulative adverse event profile will be taken into consideration when making decisions on dose escalation or de-escalation.

Any subject meeting the criteria for Hy's Law case (ie, severe drug-induced liver injury) will be considered a DLT. A Hy's Law case is defined as: AST or ALT values of $\geq 3 \times$ ULN AND with serum total bilirubin level (TBL) of $> 2 \times$ ULN without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities (see [Table 11-7](#) on hepatotoxicity management and [Section 11.8](#) for further explanation of Hy's law case and Management of Hepatic Function).

If a subject experiences a DLT during the DLT evaluation period, study treatment should be discontinued for that subject. Additionally, any treatment-related toxicity meeting the DLT definition after [REDACTED] should result in discontinuation of therapy. In subjects with PR, CR or evidence of clinical benefit (as determined by the investigator), an option to continue at the same or at a reduced dose level can be considered once the toxicity returns to the subject's baseline value or CTCAE grade ≤ 1 if deemed appropriate by the investigator and sponsor.

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

6.2.2.1 Amgen Investigational Product: AMG 256

The reason for dose withholds, dose delays and/or dose change is to be recorded on each subject's CRF.

6.2.2.2 Infusion-related/Allergic/Hypersensitivity Reactions

Infusion-related and hypersensitivity reactions may occur following the administration of AMG 256. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, rigors, flushing, urticaria, hypotension, dyspnea, wheezing, headache, back pain, and abdominal pain. If an infusion-related reaction is suspected, perform a physical examination, monitor vital signs, monitor pulse oximetry, and perform an ECG if the patient is experiencing chest pain or sustained tachycardia.

Treatment and restart guidelines for infusion reactions associated with the administration of AMG 256 are provided in [Table 11-3](#).

In each case of an infusion-related reaction, the Investigator should institute treatment measures according to the best available medical practice. In cases of anaphylaxis, epinephrine should be used immediately.

If there is an observed infusion-related/allergic/hypersensitivity reaction, the medical monitor and global study team should be contacted as soon as possible to discuss the reaction.

6.2.2.3 Coagulopathy (including Disseminated Intravascular Coagulation)

Coagulopathy, including DIC, may occur following the administration of AMG 256.

Monitor patients for signs and symptoms of high fever, hypotension, shortness of breath, confusion, severe malaise, ecchymoses, purpura, petechiae, and bleeding including at mucosal membranes. If coagulopathy adverse reactions or DIC is suspected, perform a physical examination, monitor vital signs, monitor pulse oximetry, and perform an ECG if patient is experiencing chest pain. Consider re-ordering basic labs for chemistry, hematology and coagulation parameters. Subjects should be educated on the signs and symptoms of coagulopathy associated events and asked to contact the investigator immediately if any irregular bleeding is noted (see [Appendix 13](#)). Investigators are encouraged to contact subjects between doses during cycles 1 and 2 to ensure compliance of monitoring symptoms presented in the questionnaire.

Treatment guidelines for coagulopathy associated with the administration of AMG 256 are provided in [Table 11-4](#).

6.2.2.4 Immune-related (Inflammatory) Adverse Reactions

Adverse events following the administration of AMG 256 may have an immunologic etiology. Based on clinical experience with other anti-PD-(L)1 therapies, these immune related inflammatory adverse reactions may occur shortly after the first dose to

several months after the last dose of treatment and may affect more than one body system simultaneously. Early recognition and management is critical to reduce complications.

Most immune-related adverse events require adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests, such as bronchoscopy, endoscopy, or skin biopsy, may be included as part of the evaluation.

Based on the type and severity of the immune-related adverse event, withholding or permanent discontinuation of AMG 256 may be required, in addition to treatment with corticosteroids and/or other therapies. Dose modification and toxicity management guidelines for immune-related adverse reactions are provided in [Table 11-2](#).

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to [Section 11.8](#) for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

6.4 Treatment Assignment

6.4.1 Method of Treatment Assignment

Subjects who meet eligibility criteria will be enrolled and assigned to treatment with AMG 256.

During cycles 1 and 2 of dose escalation, sites must receive written confirmation from the study team prior to all doses during cycles 1 and 2 with approval that it is safe to proceed with dosing.

6.4.2 Blinding

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

6.5 Treatment Compliance

Compliance to treatment and the corresponding assessments should be followed according to the Schedule of Activities ([Section 1.3](#)) and the Study Assessments and Procedures ([Section 8](#)).

6.6 Treatment of Overdose

The effects of overdose of this product are not known.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior therapies that were being taken/used for the disease under study will be collected from time of initial diagnosis to time of consent.

Collected line of therapy, regimen, medication, dose, unit, frequency, route, date first and last taken, reason for stopping, setting, progression date, best response and best response date to be recorded in the eCRF.

6.7.2 Concomitant Treatment

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

Concomitant therapies are to be collected from informed consent through safety follow up. Concomitant therapies collected from safety follow up through end of study are to be collected if administered to treat a reportable SAE.

Collected medication, indication, dose, unit, frequency, route, and date first and last taken are to be recorded in the eCRF.

7. Discontinuation Criteria

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

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in [Sections 7.1, 7.2.1, and 7.2.2](#).

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see [Section 1.3](#)) 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, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Disease progression
- Pregnancy

7.2 Discontinuation From the Study

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

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see [Section 11.7](#) for further details). Refer to the Schedule of Activities ([Section 1.3](#)) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

This section is not applicable.

7.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

7.3 Lost to Follow-up

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

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

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

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see [Section 1.3](#)).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

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

8.1 General Study Periods

8.1.1 Screening, Enrollment and/or Randomization

A signed and dated IRB/IEC- approved informed consent must be obtained before any study-specific procedures are performed. Procedures that are part of routine care are not considered study-specific procedures and may be used at screening to determine eligibility. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study. The screening window is up to 28 days prior to day 1.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening up to 3 additional times.

Subjects will retain the same subject identification number assigned at the original screening.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities ([Section 1.3](#)). The date of the first dose of AMG 256 is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of AMG 256 is to be administered after all safety assessments have been completed and reviewed during each visit that it is required.

8.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, safety follow-up visits will be performed approximately 30 (+7) days and 90 ($\pm$ 7) days after the last dose of AMG 256.

8.1.4 Long-term Follow-up

Subjects will be contacted 6 months ($\pm$ 1 week) after the last dose of study drug. The purpose of the calls is to collect information on adverse events, start of new therapies and disease status.

8.1.5 End of Study

The end of study will be the day of the last scheduled long term follow up call.

8.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

8.2.1 General Assessments

8.2.1.1 Informed Consent

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

8.2.1.2 Demographics

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

8.2.1.3 Medical History

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

8.2.1.4 Physical Examination

Physical examination will be performed as per standard of care by the investigator or designee at screening and at the time points specified in the Schedule of Activities ([Section 1.3](#)). The physical examination will include general appearance, including examination of the skin, spleen, respiratory, cardiovascular, musculoskeletal, and neurological systems.

The individual performing the physical examination will characterize their findings as either normal or abnormal. Abnormal physical examination findings found during screening should be reported on the Medical History eCRF. Abnormal physical examination findings found after the subject has received investigational product will be reported on the Event eCRF.

8.2.1.5 Clinical Tumor Measurements (Melanoma Subjects Only)

Visible cutaneous lesions identified as target lesions must be measured, documented digitally using standardized photographic images ([Section 8.2.3](#)) for photography including a centimeter ruler for scale, as part of the image. The exact digital image equipment, acquisition and standardized procedure will be described in the Imaging Procedural Manual provided by the central core lab. Skin lesions must be documented and assessed and at the time points specified in the Schedule of Activities ([Section 1.3](#))

8.2.1.6 Physical Measurements

Height should be measured without shoes at screening only. Weight should be measured without shoes at the time points specified in the Schedule of Activities ([Section 1.3](#)).

8.2.1.7 Performance Status

Subjects will be graded according to the Eastern Cooperative Oncology Group (ECOG) Performance Status. The ECOG criteria for this protocol are further defined in [Section 11.10](#).

8.2.2 Radiographic Assessments

Standard radiological assessments should take place until clinically significant disease progression or deterioration, withdrawal of consent, or start of new anticancer therapy. Every assessment must include contrast-enhanced CT of the chest, abdomen, pelvis, and all other known sites of disease. The assessment should include magnetic resonance imaging (MRI) of the brain if a subject has signs or symptoms suggestive of CNS metastases. The assessment can be conducted earlier if clinical deterioration necessitates an earlier scan at the discretion of the managing physician. The same contrast and modality used at screening should be used for all subsequent assessments. In order to reduce radiation exposure for subjects, low dose CT or MRI should be applied whenever possible.

Tumor burden assessments will be performed based on modified RECIST 1.1 and iRECIST. Modified RECIST 1.1 criteria will be used to determine eligibility based on the investigator's review of the radiographic data. Tumor assessments following modified RECIST 1.1 will continue through the first disease progression (PD). iRECIST will be used to account for unique tumor response characteristics observed with immunotherapies and enable treatment decisions beyond progression (per modified RECIST 1.1). Tumor burden assessment performed at sites for decisions on treatment

continuation will be based on iRECIST only and will continue until immune Confirmed Progression Disease (iCPD).

Tumor burden assessments performed by the central imaging core laboratory will be based on modified RECIST 1.1 and iRECIST.

To confirm PD, a second CT scan must be performed 4-6 weeks after the first detection of radiographical progression. Responses (partial response [PR] and complete response [CR]) require confirmation by a repeat consecutive assessment at least 4 weeks after the first detection of radiographical response. For details on imaging assessments, refer to the Imaging Manual provided by the central imaging core laboratory. If a subject continues AMG 256 treatment after confirmation of radiographic progression disease, CT/MRI assessment will be performed every 8 (± 1) weeks thereafter. Subjects must to agree to continued treatment by signing the study addendum consent. The addendum consent is to be signed after the first scan showing PD.

If a subject discontinues treatment for reasons other than progression, tumor evaluations should continue according to the Schedule of Activities ([Section 1.3](#)) until progression or start of a new treatment regimen.

8.2.3 Photography (Melanoma Subjects Only)

Color digital photographs of all visible tumors must be obtained at the time points specified in the Schedule of Activities ([Section 1.3](#)). Whole limb and whole body photographs should be taken at screening, as appropriate to document overall disease status, and at every subsequent time point. All photographs will maintain the anonymity of the patient but will identify the subject by the unique subject identification number and date of photograph. Assessment measurements using centimeter ruler will also be included in photographs so that the size of the lesion can be assessed by reviewers. Additional photographs may be taken at the discretion of the investigator at any time during the study. If vitiligo or any other clinically notable visible phenomenon appears at any time, this should be photographed with photographic follow up at each subsequent Day 1 visit until it resolves.

8.2.4 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see ([Section 1.3](#)).

8.2.4.1 Vital Signs and Pulse Oximetry

The following measurements must be performed: systolic/diastolic blood pressure (BP), respiratory rate, heart rate, pulse oximetry and temperature. Subject must be in rested

and calm state for at least 5 minutes before BP assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. Record all measurements on the vital signs eCRF.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs/temperature eCRF. Vital signs and pulse oximetry will be recorded by the investigator or designee at screening and time points specified in the Schedule of Activities ([Section 1.3](#)).

Abnormal measurements may be repeated at the discretion of the investigator and must be reported on the corresponding eCRF page. When vital signs and blood sample collection occur at the same time, vital signs and pulse oximetry should be performed before blood samples are drawn.

8.2.4.2 Electrocardiograms (ECGs)

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

All three ECGs should be completed within a total of five minutes from the start of the first to the completion of the third at the time points specified in the Schedule of Assessments ([Section 1.3](#)).

- Screening: ECGs collected in triplicate run consecutively (total 3 ECGs)
- For cycle 1 before initiation of AMG 256 dosing: 3 baseline ECGs collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (all 3 ECGs should be completed within a total of 5 minutes from the start of the first to the completion of the third) (total 9 ECGs)
- All other ECGs at time points after initiation of AMG 256 dosing collected in triplicate run consecutively (total 3 ECGs)

The PI or designated sub-investigator will review all ECGs. ECGs will be transferred electronically to a central Amgen vendor. Once reviewed and signed by the PI or sub-investigator, 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 will be provided by Amgen for all study-related ECG requirements.

8.2.4.3 Vital Status

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

8.2.5 Adverse Events and Serious Adverse Events

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

8.2.5.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and is described in [Section 11.4](#).

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product(s)/study treatment/protocol-required therapies through the safety follow-up (90 [$\pm$ 7] days after last dose of AMG 256) visit are reported using the Event CRF.

8.2.5.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the safety follow-up (90 [$\pm$ 7] days after last dose of AMG 256) visit are reported using the Event CRF.

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

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

8.2.5.1.3 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. Per local requirements in some countries, 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 and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in [Section 11.5](#).

8.2.5.2 Method of Detecting Adverse Events and Serious Adverse Events

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

8.2.5.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in [Section 7.3](#)). Further information on follow-up procedures is given in [Section 11.5](#).

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

8.2.5.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical

investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

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

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the [Investigator's Brochure](#) and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.5.5 Safety Monitoring Plan

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

8.2.5.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until 3 months after the last dose for female subjects and until 5 months after the last dose for female partners of male subjects.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in [Section 11.6](#). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in [Section 11.6](#).

8.2.6 Clinical Laboratory Assessments

Refer to [Section 11.2](#) for the list of clinical laboratory tests to be performed and to the Schedule of Activities ([Section 1.3](#)) for the timing and frequency. All tests (except for PK and biomarkers) are to be performed at a local laboratory and test results are to be recorded in the eCRF. Additional safety laboratory assessments may be performed if clinically indicated at the discretion of the investigator.

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 [Section 11.2](#), must be conducted in accordance with the laboratory manual and the Schedule of Activities ([Section 1.3](#)).

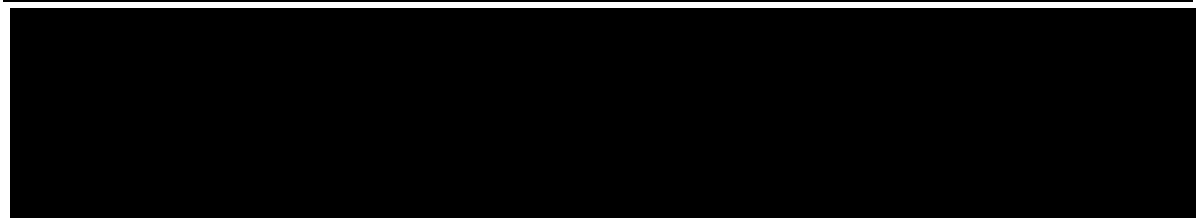
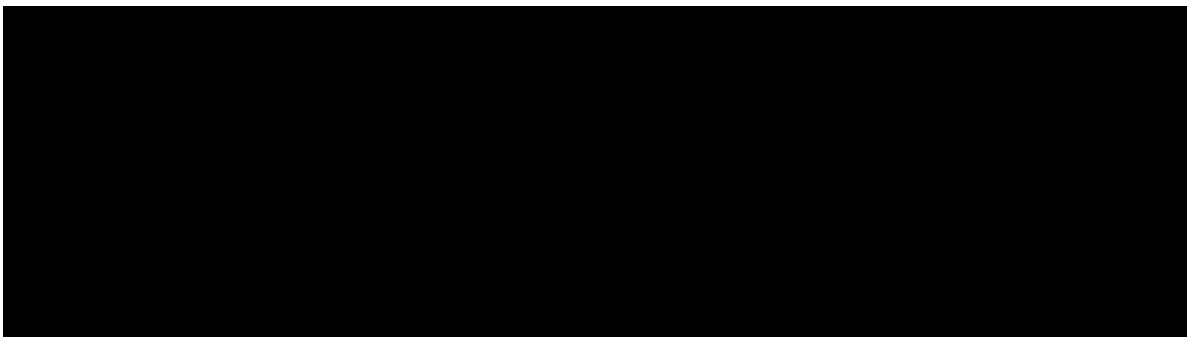
Pregnancy Testing

A serum pregnancy test should be completed at screening and within 48 hours of initiation of AMG 256 (cycle 1 day 1 dose) for females of childbearing potential.

Beginning with cycle 2, pregnancy testing (urine or serum) must be performed within 48 hours of day 1 of every cycle during treatment with AMG 256 and 30 (+7) days after the last dose of protocol-required therapies (see Schedule of Activities, [Section 1.3](#))

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

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see [Figure 11-3](#)). Refer to [Section 11.6](#) for contraceptive requirements.



The final disposition of samples will be described in [Section 11.7](#).

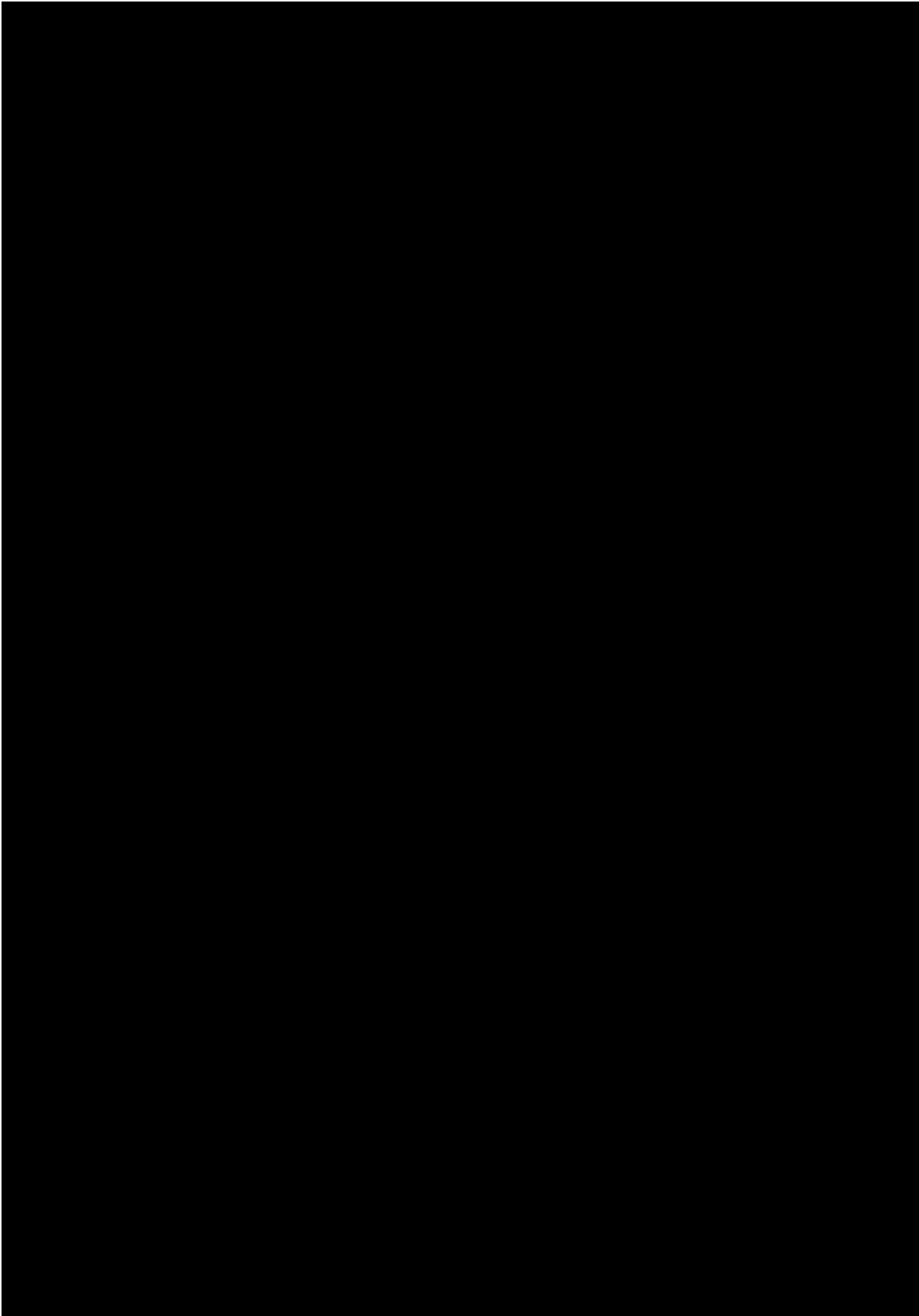
8.2.9 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities ([Section 1.3](#)) for the measurement of anti-AMG 256 binding antibodies. Samples testing positive for binding antibodies may be further characterized. Additional blood samples may be obtained to rule out anti-AMG 256 antibodies during the study.

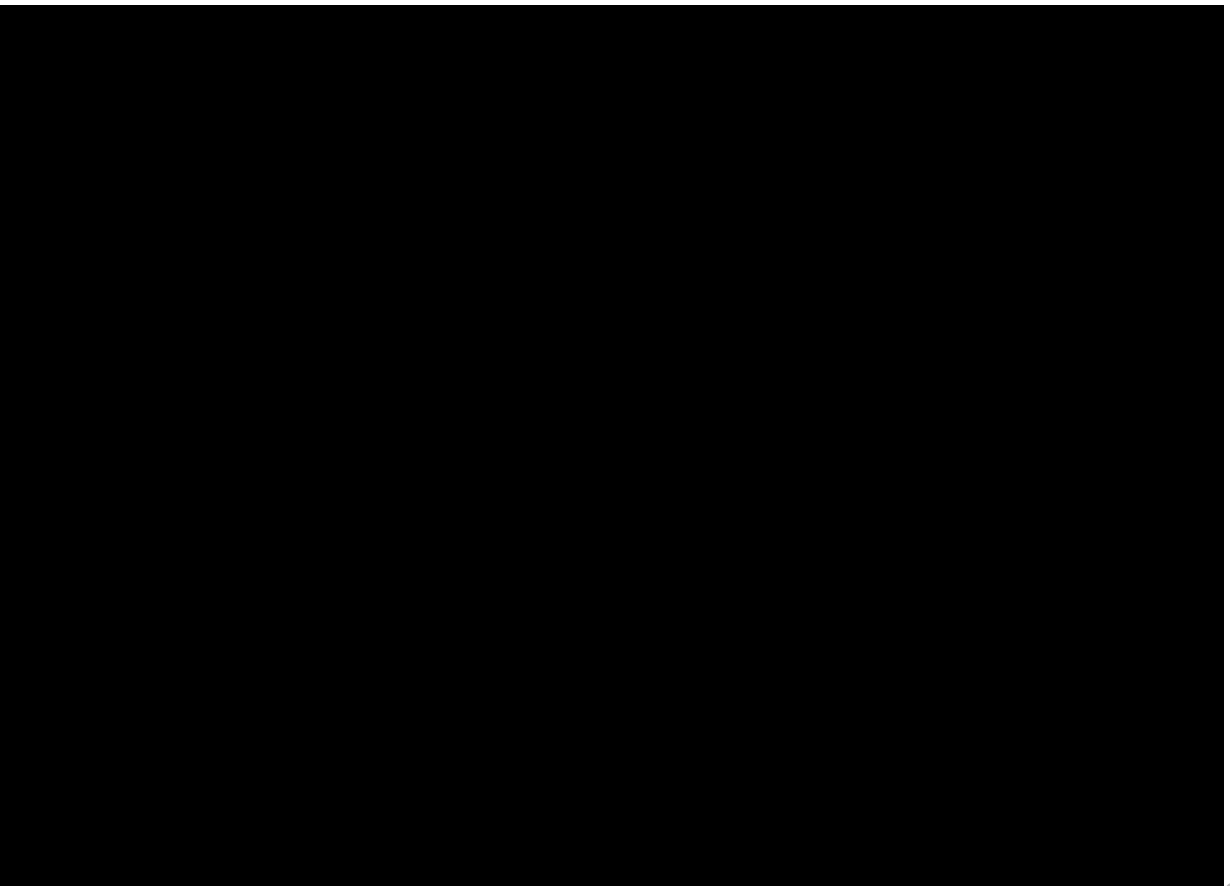
Subjects who test positive for neutralizing antibodies to IL-21 or who have anti-AMG 256 binding antibodies with potentially antibody-mediated clinical sequelae at the final scheduled study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from the safety follow up visit until: (1) antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year ($\pm$ 4 weeks) post administration of AMG 256. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Refer to the Schedule of Activities ([Section 1.3](#)), as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions.

8.2.10 Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.



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9. Statistical Considerations

9.1 Statistical Hypotheses

This is a phase 1 study and no formal statistical hypotheses will be tested.

9.2 Sample Size Determination

It is anticipated that approximately 100 subjects will be enrolled in this study.

Approximately 30 subjects will be enrolled in the dose-escalation cohorts including up to 10 additional subjects as part of backfill enrollment. Up to 60 subjects will be enrolled in the dose-expansion cohorts.

The sample size in the dose-escalation phase is based on practical consideration and is consistent with conventional oncology studies with the objective to estimate the MTD.

With 3 subjects in a cohort, there is a 27% to 70% probability of observing at least 1 DLT if the true DLT rate is 10% to 33% and with 6 subjects in a cohort, there is a 47% to 91% probability.

In the dose-expansion cohort, a subject sample size of 60 will provide a 95% probability of observing at least 1 adverse event with 5% incidence rate. An exact 95% binomial CI will be provided for overall response rate. With the 60 subjects and 20% overall

response rate, the expected 95% CI would be 11% to 32%. Under certain circumstances, the sample size dose expansion will be smaller due to early stopping; see [Section 9.4.1.1](#) for details.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 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 256.

The analysis of DLT will be conducted on the DLT Analysis set defined as all subjects that are enrolled and receive at least 1 dose of AMG 256 with an evaluable DLT endpoint. The DLT endpoint is evaluable if either: 1) the subject experiences a DLT, or 2) the subject does not experience a DLT within the DLT window.

The analysis of objective response will be conducted on the RECIST Evaluable Analysis set defined as all subjects that are enrolled to a dose expansion cohort and receive at least 1 dose of AMG 256 with at least one tumor lesion that is measurable in contrast-enhanced computed tomography (CT) as defined by RECIST 1.1, with the following exceptions. The following subjects will be excluded from the RECIST Evaluable Analysis set: 1) subjects who are lost to follow up and have no on study radiological assessments and 2) subjects who have been on study less than 8 weeks and have no on study radiological assessments.

9.3.2 Covariates

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

9.3.3 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.

9.3.4 Handling of Missing and Incomplete Data

The handling of missing and incomplete data is described in the statistical analysis plan.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To

preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in [Section 4.4.1](#).

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

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 recommendations. As a sensitivity analysis, a 1-parameter Continual Reassessment Method model may be used to estimate the dose-toxicity relationship and in particular to estimate the dose level with a 25% DLT rate in order to help make dose escalation decisions. Adverse events, including late onset immune-mediated toxicities, and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions. If during the study there is any Grade 5 adverse event (or any two of the same Grade 4 adverse events) at least possibly related to AMG 256, further accrual will be suspended; Amgen will conduct a safety analysis and submit to the regulatory authority for review prior to resuming enrollment.

Key details of the BLRM model as used in this study are as follows. A bi-variate normal prior distribution (parameters “a” and “b”) is used for the BLRM model with bi-variate normal prior are as follows: the mean natural log (ln) of “a” $\ln(a) = -0.847$, standard deviation (SD) of “a” $SD(a) = 1.275$, mean $\ln(b) = -0.727$ $SD(b) = 3.269$ and correlation = 0. The prior distribution is specified such that probability of dose-limiting toxicity (DLT) is 0.01 for the starting dose (■ mg) and 0.3 for the reference dose (■ mg), where the probability that the true DLT rate is ≤ 0.40 at the lowest planned dose is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose is 0.05. The BLRM recommended next dose level is the level with the highest probability of the target toxicity probability interval (TPI), but with a less than 0.40 probability of an excessive or unacceptable TPI.

During dose expansion, if the observed rate of responses in a tumor type is less than 10% after $n = 10$ and $n = 20$ subjects then enrollment to the tumor type will be terminated due to futility. For purposes of assessing futility, a response is defined as an

objective response per RECIST 1.1. The guidelines for early termination of enrollment for a tumor type due to futility are as follows:

Number of Treated Subjects in a Tumor Type	Enrollment Stopping Rule
10	0 responders
20	1 or fewer responders

If the true response rate is 5% then these termination guidelines result in a 78.7% probability of terminating tumor type enrollment at or prior to $n = 20$ subjects. If the true response rate is 20% then there is an 86.4% probability of continuing enrollment past $n = 20$ subjects.

During dose expansion, Amgen will conduct evaluations of the ongoing grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible early trial termination has been reached. If this threshold is met, enrollment to dose expansion will be halted pending review of safety data by the DLRT. After receiving the DLRT recommendation, Amgen will choose to take one of the following actions.

- Terminate the trial
- Amend the protocol to potentially improve the benefit/risk for subjects (eg, increase safety monitoring, modify dose/schedule, mandate premedication)
- Continue dose expansion without any changes

The stopping rules use a Bayesian approach proposed by Thall, Simon, and Estey (1995) to terminate the study if the posterior probability that the grade 4 or higher treatment-related adverse event rate is greater than 20% is $> 80\%$. The stopping boundaries assume a prior distribution of Beta (0.40, 1.60) are presented in [Table 9-1](#) and the operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in [Table 9-2](#). The operating characteristics in [Table 9-2](#) provide the probability of stopping the trial early for given hypothetical true rate of grade 4 or higher treatment-related adverse events, whereas the stopping criteria in [Table 9-1](#) are based on situations where the empirical evidence would result in the posterior probability of $\geq 80\%$ that the true grade 4 or higher treatment-related adverse event rate is $\geq 20\%$.

Table 9-1. Stopping Boundary for Dose Expansion With Posterior Probability of 80% and Grade 4 or Higher Treatment-related Adverse Event Limit of 20%

Number of subjects	Hold enrollment if observing this many grade 4 or higher treatment adverse events
10	≥ 4
20	≥ 6
30	≥ 9
40	≥ 11
50	≥ 13
60	Dose Expansion Complete

Table 9-2. Operating Characteristics With Batch Size of 10 Subjects

True grade 4 or higher treatment-related adverse event rate	Probability of early stopping of dose expansion	Average dose expansion sample size
0.10	2.1%	59.0
0.15	11.3%	55.4
0.20	33.1%	47.6
0.25	62.1%	37.0
0.30	84.8%	27.1

9.4.1.2 Primary Analysis

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

9.4.1.3 Final Analysis

The final analysis will occur when target enrollment is complete for all study parts and all 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.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, pharmacodynamic and biomarker data. Unless otherwise specified, descriptive summaries will be presented by planned dose level and schedule. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

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

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	Listings of secondary efficacy endpoints will be produced for all subjects in the dose-escalation cohorts and the dose-expansion cohorts. For all subjects in the RECIST Analysis Set, the proportion of subjects and 95% CI with an objective response (complete or partial response per RECIST 1.1 and iRECIST) or disease control (complete or partial response per RECIST 1.1 and iRECIST or stable disease per RECIST 1.1 and iRECIST lasting 16 weeks or longer) will be tabulated by tumor type and planned dose level and schedule. For all subjects in the RECIST Analysis Set, Kaplan-Meier methods will be used to estimate the time of event curve, median time to event and percentiles with 95% CI for 1) duration of overall response (DOR) 2) progression-free survival (PFS) and 3) duration of stable disease (DOSD). Kaplan-Meier methods will be used to estimate appropriate landmarks for PFS, DOR and DOSD (eg, 1-year PFS).
Exploratory	Will be described in the statistical analysis plan finalized before database lock

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the safety analysis set, which includes subjects that are enrolled and received AMG 256. The analysis of DLTs will be conducted on the DLT Analysis Set. Subject incidence of DLT will be tabulated by planned dose level. A table of DLT will be provided. The probability of a subject having a DLT by dose level will be estimated using a two-parameter BLRM model. The statistical analysis methods for other safety endpoints are described in Section 9.

9.4.2.3.2 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment emergent adverse events will also be provided. Subject incidence of device-related events, if applicable, will be tabulated by system organ class and preferred term.

9.4.2.3.3 Laboratory Test Results

Clinical chemistry, hematology, and urinalysis data will be reviewed for each subject. Depending on the size and scope of changes in laboratory data the analyses of safety laboratory endpoints will include summary statistics over time and/or changes from baseline over time may be provided. Shifts in grades of safety laboratory values from baseline for selected laboratory values may also be provided.

9.4.2.3.4 Vital Signs

Vital signs data will be reviewed for each subject. The analyses of vital signs will include summary statistics over time and/or changes from baseline over time may be provided.

9.4.2.3.5 Physical Measurements

Physical measurements will be reviewed for each subject.

9.4.2.3.6 Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QTcF will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized. All on-study ECG data will be listed and select parameters of interest plotted.

9.4.2.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 256 antibodies at any time will be tabulated by treatment group.

9.4.2.3.8 Exposure to Investigational Product

Details of AMG 256 administration will be listed for every subject.

9.4.2.3.9 Exposure to Non-investigational Product

Not applicable.

9.4.2.3.10 Exposure to Other Protocol-required Therapy

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug dictionary.

9.4.2.3.11 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug dictionary.

9.4.2.4 Other Analyses

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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Approved

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
AUC	Area under the plasma concentration time curve
CFR	U.S. Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C _{max}	Maximum observed plasma concentration
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DES	Amgen data element standard
DILI	drug induced liver injury
DLRM	Dose level review meeting
DLRT	dose level review team
DLT	dose limiting toxicity
ECG	electrocardiogram
Echo	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
Enrollment	When investigator decides that the subject has met all eligibility criteria
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable

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
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
IBG	Independent Biostatistics Group
ICF	informed consent form
ICH	International Conference on Harmonisation
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
LVEF	left ventricular ejection fraction
MTD	maximum tolerated dose
MUGA scan	multigated acquisition scan
NCT	National Clinical Trials
PK	Pharmacokinetic(s)
RP2D	Recommended phase 2 dose
SAT	safety assessment team
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
TBL	total bilirubin
t_{max}	time to maximum observed plasma concentration
SUSAR	suspected unexpected serious adverse reaction
TMF	trial master file
ULN	upper limit of normal

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11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in [Table 11-1](#) will be performed by the local laboratory (unless specified otherwise).

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

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

Table 11-1. Analyte Listing

Local Laboratory: Chemistry	Local Laboratory: Coagulation	Local Laboratory: Urinalysis	Local Laboratory: Hematology	Other Labs
Sodium	PT	Specific gravity	RBC	<u>Central Laboratory:</u>
Potassium	APTT/INR	pH	Hemoglobin	Antibodies
Chloride	Fibrinogen	Blood	Hematocrit	
Bicarbonate	D-dimer	Protein	MCV	
Total protein	FDP	Glucose		
Albumin		Bilirubin	Platelets	
Calcium		WBC	WBC	
Adjusted calcium		RBC	Differential	
Magnesium		Epithelial cells	• Total	
Phosphate		Bacteria	Neutrophils	
Glucose		Casts	• Eosinophils	
BUN or Urea		Crystals	• Basophils	<u>Local Laboratory:</u>
Creatinine			• Lymphocytes	Serum or Urine
Total bilirubin			• Monocytes	Pregnancy
Direct bilirubin				Hep B surface antigen
ALP				Hep B core antibody
LDH				Hep C antibody
AST (SGOT)				HIV
ALT (SGPT)				ACTH
TSH				ANA
Free T4				ANCA
Uric Acid				(cytoplasmic and perinuclear)

ACTH = Adenocorticotrophic hormone; ANA = Antinuclear Antibodies; ANCA = Antineutrophil cytoplasmic antibodies; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FDP = fibrin/fibrinogen degradation products; HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count

11.3 Appendix 3. Study Governance Considerations

Committee(s)

Dose Level Review Meeting (DLRM)

A DLRM is conducted to review and interpret safety data for the purposes of making recommendations about dose-level escalation (either to the next planned dose or to an intermediate dose), dose level de-escalation, cohort continuation, or cohort expansion; making recommendations about non-dose escalation cohorts (eg, expanded, highest dose and/or final cohort); and evaluating safety signals for purposes of applying Dose Cohort Stopping Rules. The required Dose Level Review Team (DLRT) members are the Medical Monitor, Global Safety Officer (GSO), and Site Investigators. The DLRT will include all Site Investigators. The Medical Monitor, GSO, and Site Investigators are the only voting DLRT members. The following non-voting Amgen representatives may also be part of the DLRT: safety scientist, global study manager, biostatistician, PK scientist.

The Medical Monitor must be in attendance and cannot be represented by a voting designee or delegate. Voting designees can be identified as appropriate by the GSO or Site Investigator(s). A Site Investigator may identify a delegate (eg, sub-Investigator) who is listed in the Delegation of Authority.

For a DLRM to occur, the Medical Monitor must attend, and the GSO or delegate must attend. In addition, a quorum of Site Investigators must be present. A quorum is defined as more than 50% of the participating investigators or their qualified designee. The DLRM will be rescheduled if these requirements are not met.

All available study data, including demographics, IP administration, medical history, concomitant medications, adverse events, late onset immune-mediated toxicities, ECG, vital signs, and laboratory results will be reviewed. Data to be reviewed will be unqueried.

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

DLRM recommendations to escalate to the next planned cohort, or to an intermediate cohort, must be made by unanimous vote. If the voting members of the DLRT are not able to reach a unanimous recommendation on whether to escalate to the next planned

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

Regulatory and Ethical Considerations

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

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

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

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

Site staff may identify potential subjects from their existing patient population and/or may seek referral patients through existing professional networks or other community sources. All patient-facing materials must be reviewed/approved by the sponsor (Amgen Inc.) and the local IRB/IEC prior to use.

Informed Consent Process

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 sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care

physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the 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. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to [Section 7](#).

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study, if applicable.

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

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the 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. (Refer to ICH GCP guideline, Section 4.8.9.)

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

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

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Data Protection/Subject Confidentiality

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

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

On the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

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

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

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

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

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

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

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

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or

adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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

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

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

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

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

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

Source Documents

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

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

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

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

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, 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, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

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

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

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

Compensation

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

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11.4 Appendix 4. Toxicity Management Guidelines

Table 11-2. Dose Modification and Toxicity Management Guidelines for Immune-related (Inflammatory) Adverse Reactions Associated With AMG 256

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 256 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Pneumonitis	Grade 2 (symptomatic, involves more than one lobe of the lung of 25-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider additional immunosuppressive agent (eg, infliximab, mycophenolate, cyclophosphamide) if refractory to corticosteroids.	Monitor subjects for signs and symptoms of pneumonitis. Evaluate subjects with suspected pneumonitis with radiographic imaging. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 (severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated)	Permanently discontinue		
	Grade 4 (life-threatening respiratory compromise, urgent intervention indicated [intubation])			

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Footnotes defined on last page of this table

Table 11-2. Dose Modification and Toxicity Management Guidelines for Immune-related (Inflammatory) Adverse Reactions Associated With AMG 256

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 256 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Colitis/Diarrhea	Grade 2 (increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared with baseline)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider infliximab if symptoms refractory to corticosteroids within 2-3 days.	Monitor subjects for signs and symptoms of enterocolitis (eg, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (eg, peritoneal signs and ileus). For subjects with grade ≥ 2 diarrhea suspecting colitis, consider GI consultation and endoscopy to rule out colitis.
	Grade 3 (increase of 7 or more stools per day over baseline, incontinence; hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL)			
	Grade 4 (life-threatening consequences; urgent intervention indicated)	Permanently discontinue		

Footnotes defined on last page of this table

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Table 11-2. Dose Modification and Toxicity Management Guidelines for Immune-related (Inflammatory) Adverse Reactions Associated With AMG 256

Immune-Related Adverse Reactions	AMG 256 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Hepatitis	Refer to Section 11.8 Appendix 8. Hepatotoxicity Stopping Rules for criteria for withholding or permanently discontinuing AMG 256 treatment (Table 11-7) based on laboratory values, clinical signs/symptoms	Administer corticosteroids at an initial dose of 0.5 to 2 mg/kg/d prednisone (or equivalent) followed by taper.	Monitor with liver function tests more frequently until returned to baseline or stable.

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Table 11-2. Dose Modification and Toxicity Management Guidelines for Immune-related (Inflammatory) Adverse Reactions Associated With AMG 256

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 256 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Hypophysitis	Grade 3 or 4 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Administer corticosteroids at an initial dose of 1 mg/kg/d prednisone (or equivalent) followed by taper. In addition, initiate hormonal replacement therapy as clinically indicated.	Monitor for signs and symptoms of hypophysitis. Consider endocrine consultation.
Adrenal Insufficiency	Grade 3 or 4 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Initiate IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg [if the diagnosis is not clear and ACTH stimulation testing will be needed]). Taper stress-dose corticosteroids down to maintenance doses (prednisone 5 to 10 mg daily) over 1-2 weeks after discharge.	Monitor for signs and symptoms of adrenal insufficiency. Consider endocrine consultation.
Hypothyroidism	Grade 3 or 4 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Initiate thyroid hormone supplementation.	Monitor subjects for signs and symptoms of hypothyroidism. Consider endocrine consultation.
Hyperthyroidism	Grade 3 or 4 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Initiate β -Blocker (eg, atenolol, propranolol) for symptomatic relief. For severe symptoms or concern for thyroid storm, initiate prednisone 1-2 mg/kg/d (or equivalent) tapered over 1-2 weeks. Consider use of SSKI or thionamide (methimazole or PTU).	Monitor subjects for signs and symptoms of hyperthyroidism. Consider endocrine consultation.

Table 11-2. Dose Modification and Toxicity Management Guidelines for Immune-related (Inflammatory) Adverse Reactions Associated With AMG 256

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 256 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Diabetes Mellitus	Grade 3 hyperglycemia (> 250 to 500 mg/dL [> 13.9 to 27.8 mmol/L])	Withhold	Initiate insulin therapy.	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes. Consider endocrine consultation.
	Grade 4 hyperglycemia (> 500 mg/dL [> 27.8 mmol/L])			
Nephritis and Renal Dysfunction	Grade 2 (serum creatinine >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN)	Withhold	Administer corticosteroids at an initial dose of 0.5 to 1 mg/kg/d prednisone (or equivalent) followed by taper. If worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/d prednisone (or equivalent).	Monitor changes in renal function. Evaluate for other causes of renal dysfunction (eg, recent IV contrast, medications, fluid status, etc)
	Grade 3 (serum creatinine >3.0 x baseline; >3.0 - 6.0 x ULN)	Permanently discontinue	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper.	
	Grade 4 (serum creatinine > 6 x ULN; dialysis indicated)			

Footnotes defined on last page of this table

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Table 11-2. Dose Modification and Toxicity Management Guidelines for Immune-related (Inflammatory) Adverse Reactions Associated With AMG 256

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 256 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids as indicated.	Monitor subjects for suspected severe skin reactions and exclude other causes (eg, infection, an effect of another drug, a skin condition linked to another systemic disease, etc). For signs or symptoms of SJS or TEN, withhold study drug and refer the patient for specialized care for assessment and treatment.
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue		
Encephalitis	Grade 2 (moderate symptoms, some interference with ADL)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results obtained and negative for aseptic meningitis.	Monitor subjects for neurologic symptoms and exclude other etiologies (eg, infectious). Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.
	Grade 3 or 4 (severe symptoms, limiting self-care and aids warranted)	Permanently discontinue		

Footnotes defined on last page of this table

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Table 11-2. Dose Modification and Toxicity Management Guidelines for Immune-related (Inflammatory) Adverse Reactions Associated With AMG 256

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 256 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Myocarditis	Grade 1 (abnormal cardiac biomarker testing, including abnormal ECG)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper.	Monitor patients with cardiovascular symptoms. Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 2 (abnormal screening tests with mild symptoms)			
	Grade 3 (moderately abnormal testing or symptoms with mild activity)	Permanently discontinue		
	Grade 4 (moderate to severe decompensation, IV medication or intervention required, life-threatening conditions)			
All Other Immune-Related Adverse Reactions	Grade 3 adverse reaction involving a major organ	Withhold	Based on type and severity of adverse reaction, administer corticosteroids. Refer to ASCO Clinical Practice Guidelines for additional recommendations.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Life-threatening or Grade 4 adverse reaction involving a major organ	Permanently discontinue		

Table 11-2. Dose Modification and Toxicity Management Guidelines for Immune-related (Inflammatory) Adverse Reactions Associated With AMG 256

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 256 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Recurrent or Persistent Immune-Related Adverse Reactions	Recurrence of same Grade 3 or Grade 4 adverse reaction	Permanently discontinue	Based on type and severity of adverse reaction, administer corticosteroids. Additional immunosuppressive treatment may be required.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Requirement for ≥ 10 mg/day prednisone (or equivalent) for more than 12 weeks			
	Persistent grade 2 or 3 adverse reactions lasting 12 weeks or longer after last dose (ie, does not resolve to grade 0 or 1 within 12 weeks)			
<u>General considerations:</u> • Corticosteroid taper should be initiated upon improvement of signs/symptoms and/or laboratory values to Grade 1 or less. Continue corticosteroid taper over the course of at least 4 to 6 weeks. • If AMG 256 has been withheld, treatment with AMG 256 may be resumed after adverse event (or associated signs/symptoms/laboratory parameters) has been reduced to Grade 1 or less and corticosteroid has been tapered to prednisone < 10 mg (or equivalent). • For severe and life-threatening immune-related adverse reactions, IV corticosteroids should be initiated first followed by oral corticosteroids. Other immunosuppressive treatment should be initiated if the event cannot be controlled by corticosteroids.				

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* Recommendations adapted from the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines for the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy (JCO 2018)

Table 11-3. Dose Modification and Toxicity Management Guidelines for Hypersensitivity & Infusion-related Reactions

Grade	AMG 256 Dose Modification	Specific Management	Restart Guidance
1	Slow the rate of the infusion. If clinical signs/symptoms continue, then stop the infusion. In case of suspected hypersensitivity, immediately interrupt infusion.	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Treat per institutional guidelines. • If the patient is experiencing chest pain or sustained tachycardia, perform an ECG	• <i>Restart guidance for grade 1 or grade 2 infusion-related / hypersensitivity reactions:</i> • Restart possible if event successfully managed and resolves within 7 days. Amgen Medical Monitor must be consulted prior to restart of treatment. If criteria met for restart, then follow the instructions below. • If the infusion was stopped during administration, continue treatment with next scheduled infusion, do not resume prior infusion. • Minimum hospitalization for restart (administration of the next dose): 48 hours
2	Immediately stop the infusion (if applicable).	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, and narcotics. • If the patient is experiencing chest pain or sustained tachycardia, perform an ECG	• All patients at the first restart dose and all subsequent doses, must be premedicated. Premedication may consist of IV or oral diphenhydramine hydrochloride 12.5 mg and famotidine 20 mg (or similar agent) 30 to 60 minutes prior to each AMG 256 dose, or per institutional guidelines, to mitigate allergic/hypersensitivity reaction(s). • Consider premedication with dexamethasone 10 mg IV, if clinically warranted. • Conduct additional assessments as indicated in Section 6.2.2.2
≥ 3	Immediately stop the infusion (if applicable) and permanently discontinue AMG 256 treatment	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids, and epinephrine. • If the patient is experiencing chest pain or sustained tachycardia, perform an ECG • In cases of anaphylaxis, epinephrine should be used immediately.	N/A

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Table 11-4. Dose Modification and Toxicity Management Guidelines for Disseminated Intravascular Coagulopathy

Grade	AMG 256 Dose Modification	Specific Management	Restart guidance
2 (laboratory findings without bleeding)	Assess whether treatment interruption or delay is clinically appropriate, considering all signs/symptoms and laboratory trends	Treat per institutional guidelines and standard of care	If treatment was withheld, consider restart when clinically appropriate, considering all signs, symptoms, and laboratory trends. For restart, follow the instructions below. If the dose was withheld for ≥ 14 days, permanently discontinue AMG 256. - If treatment restart is delayed by ≤ 72 hours from the original scheduled dose, then the dose may be administered. The subsequent infusion should be administered after 7 (± 1) days. - If treatment restart is delayed by > 72 hours from the original scheduled dose, skip the infusion and resume treatment with the next scheduled dose.
3 (laboratory findings & bleeding)	Immediately stop the infusion (if applicable) Interruption/delay required until event has improved to grade < 2 Permanently discontinue if grade 3 event recurs	Treat per institutional guidelines and standard of care	If the event resolves to $< \text{grade } 2$ within 14 days, the investigator may restart AMG 256 if clinically appropriate and in consultation with the Medical Monitor. For restart, follow the instructions below. If the event does not resolve to $< \text{grade } 2$ within 14 days, permanently discontinue AMG 256. - If treatment restart is delayed by ≤ 72 hours from the original scheduled dose, then the dose may be administered. The subsequent infusion should be administered after 7 (± 1) days. - If treatment restart is delayed by > 72 hours from the original scheduled dose, skip the infusion and resume treatment with the next scheduled dose. - Minimum hospitalization for restart (administration of the next dose): 24 hours
4 (Life-threatening consequences; urgent intervention indicated)	Immediately stop the infusion (if applicable) and permanently discontinue AMG 256 treatment	Treat per institutional guidelines and standard of care	N/A

Table 11-5. Dose Modification and Toxicity Management Guidelines for Any Other AMG 256-related Reactions Not Meeting DLT Criteria

Grade	AMG 256 Dose Modification	Specific Management	Restart Guidance
≥ 3	Interruption/delay required if deemed intolerable and/or clinically significant by the subject or investigator and not responding to appropriate medical management until event has improved to grade ≤ 1 Permanently discontinue if: If subject missed more than 2 consecutive doses OR In case of reappearance of same event at grade 4 OR In case of repeat grade ≥ 3 event despite dose reduction	Treat per institutional guidelines and standard of care	- Restart possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. If criteria met for restart, then follow the instructions below. - If the infusion was stopped during drug administration, continue treatment with next scheduled infusion, do not resume prior infusion. - If treatment restart is delayed by ≤ 72 hours from the original scheduled dose, then the dose may be administered. The subsequent infusion should be administered after 7 (± 1) days. - If treatment restart is delayed by > 72 hours from the original scheduled dose, skip the infusion and resume treatment with the next scheduled dose.

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Table 11-6. Dose Modification and Toxicity Management Guidelines for Any Other AMG 256-related Reactions Not Meeting DLT Criteria

Grade	AMG 256 Dose Modification	Specific Management	Restart Guidance
4	Interruption/delay required if deemed intolerable by the subject or investigator and not responding to appropriate medical management until event has improved to grade ≤ 1 Permanently discontinue if: If subject missed more than 4 consecutive doses OR In case of reappearance of same event at grade 4	Treat per institutional guidelines and standard of care	- Restart possible if successfully managed and improvement to $\leq$ grade 1 in ≤ 28 days. If criteria met for restart, follow the instructions below. - If the infusion was stopped during drug administration, continue treatment with next scheduled infusion, do not resume prior infusion. - If treatment restart is delayed by ≤ 72 hours from the original scheduled dose, then the dose may be administered. The subsequent infusion should be administered after 7 (± 1) days. - If treatment restart is delayed by > 72 hours from the original scheduled dose, skip the infusion and resume treatment with the next scheduled dose.

Dose Modification and Toxicity Management Guidelines for Hepatotoxicity

- For Stopping and Rechallenge Rules please refer to [Section 11.8](#).

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11.5 Appendix 5. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

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

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Events NOT Meeting the Adverse Event Definition

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

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:

Results in death (fatal)

Immediately life-threatening

The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires in-patient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:

Is a congenital anomaly/birth defect

Other medically important serious event

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

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

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (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 (or toxicity defined below);
 - Assessment of relatedness to investigational product; and
 - Action taken.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event CRF
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The **Common Terminology Criteria for Adverse Events**, version 5.0 which is available at the following location:

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

Assessment of Causality

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

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Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

- The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form.
- If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Contingency Report Form (see [Figure 11-1](#)) within 24 hours of the investigator's knowledge of the event.
- The site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see [Figure 11-2](#))

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Figure 11-1. Sample Electronic Serious Adverse Event Contingency 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 hospitalization. **This is a mandatory field.**

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

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

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

Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:

- Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

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

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

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**

- Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

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

4. Hospitalization

If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did

not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

FORM-056006

Instructions Page 1 of 2

Version 7.0 Effective Date: 1 February 2016

Approved

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.

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.

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Figure 11-2. Sample Serious Adverse Event Report Form

AMGEN Study # 20180144 AMG 256	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 																																																							
Reporter 	Phone Number () () () 																																																							
Fax Number () () () 																																																								
2. SUBJECT INFORMATION																																																								
Subject ID Number 	Age at event onset 																																																							
Sex ☐ F ☐ M	Race 																																																							
If applicable, provide End of Study date 																																																								
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.	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 15%;">Date Started</th> <th style="width: 15%;">Date Ended</th> <th style="width: 10%;">Check only if event occurred before first dose of IP</th> <th style="width: 10%;">Is event serious?</th> <th style="width: 10%;">If serious, enter Serious Criteria code (see codes below)</th> <th style="width: 20%;">Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?</th> <th style="width: 10%;">Outcome of Event Resolved Not resolved Fatal Unknown</th> <th style="width: 10%;">Check only if event is related to study procedure eg, biopsy</th> </tr> <tr> <td>Day Month Year</td> <td>Day Month Year</td> <td></td> <td>☐ Yes ☐ No</td> <td></td> <td> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th>AMG 256</th> <th><<Device>></th> <th><<Device>></th> <th><<Device>></th> <th><<Device>></th> <th><<Device>></th> <th><<Device>></th> <th><<Device>></th> </tr> <tr> <td>No</td><td>Yes</td><td>No</td><td>Yes</td><td>No</td><td>Yes</td><td>No</td><td>Yes</td> </tr> </table> </td> <td></td> </tr> <tr> <td></td><td></td><td></td><td>☐ Yes ☐ No</td><td></td><td></td><td></td><td></td> </tr> <tr> <td></td><td></td><td></td><td>☐ Yes ☐ No</td><td></td><td></td><td></td><td></td> </tr> <tr> <td></td><td></td><td></td><td>☐ Yes ☐ No</td><td></td><td></td><td></td><td></td> </tr> </table>	Date Started	Date Ended	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 Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy	Day Month Year	Day Month Year		☐ Yes ☐ No		<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th>AMG 256</th> <th><<Device>></th> <th><<Device>></th> <th><<Device>></th> <th><<Device>></th> <th><<Device>></th> <th><<Device>></th> <th><<Device>></th> </tr> <tr> <td>No</td><td>Yes</td><td>No</td><td>Yes</td><td>No</td><td>Yes</td><td>No</td><td>Yes</td> </tr> </table>	AMG 256	<<Device>>	<<Device>>	<<Device>>	<<Device>>	<<Device>>	<<Device>>	<<Device>>	No	Yes	No	Yes	No	Yes	No	Yes					☐ Yes ☐ No								☐ Yes ☐ No								☐ Yes ☐ No				
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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: 	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 15%;">Date of Initial Dose</th> <th style="width: 15%;">Date of Dose</th> <th style="width: 10%;">Dose</th> <th style="width: 10%;">Route</th> <th style="width: 10%;">Frequency</th> <th style="width: 20%;">Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld</th> <th style="width: 20%;">Lot # and Serial #</th> </tr> <tr> <td>Day Month Year</td> <td>Day Month Year</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td><td></td><td></td><td></td><td></td><td></td><td> Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown </td> </tr> <tr> <td></td><td></td><td></td><td></td><td></td><td></td><td> Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown </td> </tr> <tr> <td></td><td></td><td></td><td></td><td></td><td></td><td> Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown </td> </tr> </table>	Date of Initial Dose	Date of Dose	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #	Day Month Year	Day Month Year												Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown																				
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AMG 256 ☐ open label	<<IP/Device>> ☐ blinded ☐ open label																																																							

FORM-056006

Page 1 of 3

Version 7.0 Effective Date: 1 February 2016

AMGEN Study # 20180144 AMG 256	Electronic Serious Adverse Event Contingency Report Form For Restricted Use
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				Site Number				Subject ID Number															
6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:																							
Medication Name(s)				Start Date			Stop Date			Co-suspect		Continuing		Dose		Route		Freq.		Treatment Med			
				Day	Month	Year	Day	Month	Year	No✓	Yes✓	No✓	Yes✓							No✓	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:																							
Test																							
Unit																							
Date																							
Day	Month	Year																					
9. OTHER RELEVANT TESTS (diagnostics and procedures) Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:																							
Date		Additional Tests										Results						Units					
Day	Month	Year																					

Approved

AMGEN Study # 20180144 AMG 256	Electronic Serious Adverse Event Contingency Report Form <u>For Restricted Use</u>
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		Site Number					Subject ID Number											
10. CASE DESCRIPTION <i>(Provide narrative details of events listed in section 3)</i> Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.																		
Signature of Investigator or Designee - _____ <i>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.</i>											Title				Date			

Approved

11.6 Appendix 6. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and female subjects of childbearing potential are outlined in [Section 5.2](#).

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 3 months after the last dose of AMG 256 for females and 5 months after the last dose of AMG 256 for female partners of male subjects.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
 - Documented hysterectomy;
 - Documented bilateral salpingectomy; or
 - Documented bilateral oophorectomy.

Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

- Premenarchal female
- Postmenopausal female
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
 - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Approved

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

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

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 5 months after the last dose of protocol-required therapies

The female partner should consider using an acceptable method of effective contraception such as: hormonal, IUD, IUS, female barrier method (diaphragm, cap, sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]).

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

Unacceptable Methods of Birth Control for Male and Female Subjects

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

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)

- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the last dose of AMG 256.
- Information will be recorded on the Pregnancy Notification Form (see [Figure 11-3](#)). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the last dose of AMG 256 of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in [Section 11.4](#). While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see [Section 7.1](#) for details).

Approved

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 5 months after the last dose of AMG 256 after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see [Figure 11-3](#)) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 3 months after the last dose of AMG 256.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 221.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 3 months after discontinuing protocol-required therapies.

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Amgen Proprietary - Confidential

AMGEN[®] Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20180144

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm ____/dd ____/yyyy ____

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

If yes, provide product (or study drug) stop date: mm ____/dd ____/yyyy ____

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

5. Breast Feeding Information

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

If No, provide stop date: mm ____/dd ____/yyyy ____

Infant date of birth: mm ____/dd ____/yyyy ____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

FORM-115201

Version 1.0

Effective Date: 24-Sept-2018

11.7 Appendix 7. Sample Storage and Destruction

Any blood, biomarker, pharmacokinetics (PK), and biopsy sample collected according to the Schedule of Activities (Table 1-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the advanced solid tumors, the dose response and/or prediction of response to AMG 256, 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 blood, serum and tumor samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the

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

Approved

11.8 **Appendix 8. 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 11-7. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
INR	--	OR > 1.5x (for subjects not on anticoagulation therapy)
AST/ALT	OR > 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)	AND In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
ALP	OR > 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 is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in [Table 11-7](#)) 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 11.5](#).

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in [Table 11-7](#) 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.

Approved

11.9 Appendix 9. ECOG Performance Status and NYHA Classification

Eastern Cooperative Oncology Group Performance Scale

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

Source: [Oken et al, 1982](#)

New York Heart Association Functional Classification

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Approved

Every week dosing scenario (minimum and staggering)

[illegible]

Indicates completion of DLT period for the last subject enrolled to the cohort

Subjects in each multiple subject cohort will be enrolled sequentially, with:

- A minimum of [REDACTED] between the first and second subjects being dosed within a cohort
- A minimum of [REDACTED] between the second, third and fourth subjects being dosed within a cohort

All efforts should be made to maintain stagger within a cohort for at least the first 8 doses (2 cycles) to minimize the potential for multiple subjects experiencing hypersensitivity reactions on the same day

AMG 256 will be administered over [REDACTED] during cycles 1 and 2; [REDACTED] during cycle 3; [REDACTED] during cycle 4 and all subsequent cycles

Observation period will be [REDACTED] after each infusion during cycles 1 and 2; and [REDACTED] after each infusion during cycle 3 and all subsequent cycles.

For multi-subject cohorts in dose escalation, sites must receive written confirmation from the study team prior to all doses during cycles 1 and 2 with approval that it is safe to proceed with dosing.

During cycles 1 and 2 for multi-subject cohorts in dose escalation, sites must notify the study team when a subject has been dosed and if subject experienced any significant adverse reaction (ie, infusion-related reaction or hypersensitivity reaction).

[illegible]

During cycles 1 and 2 for multi-subject cohorts in dose escalation, sites must notify the study team when a subject has been dosed and if subject experienced any significant adverse reaction (ie, infusion-related reaction or hypersensitivity reaction).

Approved

11.11 Appendix 11. Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (Modified RECIST 1.1)

This study utilizes modified RECIST 1.1 criteria, which includes required confirmation of disease progression, and the following modification to RECIST 1.1:

- Up to 5 target lesions per organ and 10 total are allowed (compared to 2 per organ and 5 total for standard RECIST 1.1) to increase lesion sampling and reduce assessment error.

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.

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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”).

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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.

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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 than 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.

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11.12 Appendix 12. Immune Response Evaluation Criteria in Solid Tumors (iRECIST)

Immune Response Criteria in Solid Tumors (iRECIST) ([Seymour et al, 2017](#)) is a modification of RECIST 1.1 ([Eisenhauer et al, 2009](#)) for use in cancer immunotherapy trials. The RECIST working group published iRECIST to address response patterns specific to immunotherapies, including late and durable responses after having met progressive disease (PD) according to RECIST 1.1.

The present document is not meant to be an exhaustive teaching tool on iRECIST. Instead it is meant to outline the concepts and differences between iRECIST and RECIST 1.1.

The tumor evaluations are exactly the same for RECIST 1.1 and iRECIST, except for the timepoint response nomenclature, until PD has been reached. For example, if a PR is identified at timepoint 2 for RECIST 1.1, this is called iPR at the same timepoint with the exact same measurements utilized. Only when the patient reaches RECIST 1.1 PD do the timepoint assessment processes begin to differ.

iRECIST Disease Categories

The iRECIST criteria define measurable disease, non-measurable disease, target-lesions, and non-target lesions using RECIST 1.1 definitions:

- Measurable lesions:
 - Non-nodal lesions must be ≥ 10 mm in the longest diameter
 - Nodal lesions must be ≥ 15 mm in the short axis
- A maximum of five measurable lesions (two per organ) can be target lesions
- All other disease is considered non-target (nodal lesions must be ≥ 10 mm in the short axis to be considered pathological)

At baseline, disease is categorized as target or non-target per RECIST 1.1. The same definitions and measurement types are applied to iRECIST assessments. Target lesions are measured uni-dimensionally and non-target lesions are assessed qualitatively.

New lesions are identified per RECIST 1.1 definitions, but are further categorized per iRECIST as new target lesions and new non-target lesions:

- New iRECIST target lesions must measure ≥ 10 mm in longest diameter (new nodal lesions must be ≥ 15 mm in the short axis)
- All other new iRECIST lesions are new non-target lesions (nodal lesions must be ≥ 10 mm in short axis to be considered pathological)

iRECIST recommends measuring up to five new target lesions. The requirement to measure new lesions starts at the time point of RECIST 1.1 PD. Measurement of more than five new lesions is optional and considered exploratory.

iRECIST Calculations

The iRECIST criteria requires the calculation of target lesion sum of measures (SOM) and new target lesion sum of measures (SOM). These are two distinct sums:

- **Target lesion SOM** is calculated by summing the longest diameter of target lesions (and/or short axis of target nodes). **Note:** This is the same calculation performed for RECIST 1.1 and labeled sum of diameters (SOD).
- **New target lesion SOM** is calculated by summing the longest diameter of new target lesions (and/or short axis of new target lesion nodes).

Tumor Response Assessment

The prefix “i,” meaning immune, is used to differentiate iRECIST responses from RECIST 1.1 responses.

The overall response at the time point of RECIST 1.1 PD is assessed as immune unconfirmed progressive disease (iUPD) per iRECIST initiating application of the iRECIST criteria.

After the initial iUPD assessment per iRECIST, the following guidelines apply:

- iUPD → followed by tumor shrinkage = iCR, iPR, or iSD
- iUPD → followed by worsening = iCPD
- iUPD → followed by no change = iUPD

When iUPD is followed by tumor shrinkage, this is referred to as “resetting the bar” and is one of the most important concepts of iRECIST. A subject cannot be assessed as iCPD at the time point immediately after “resetting the bar.” Disease must again qualify for iUPD, then worsen to be assessed as iCPD.

iRECIST tumor response assessments of iCR and iPR are made with reference to the original baseline time point for the subject, acquired during the study screening period. The nadir, or a subject’s best response on study, is used as the comparator when assessing for iUPD. iCPD is assessed with reference to the iUPD assessment being confirmed.

Target Lesion Assessments

The table within this section defines target lesion assessments per iRECIST.

Table 11-8. iRECIST Target Lesion Assessments

iRECIST Target Lesion Assessments	Requirements
Immune Complete Response (iCR)	Requires disappearance of all non-nodal target lesions and normalization of pathological target lymph nodes to < 10 mm in short axis
Immune Partial Response (iPR)	Requires $\geq 30\%$ decrease in sum of measures of target lesions, taking as reference the baseline target lesion sum The reference time point is the subject's original baseline time point acquired during the study screening period
Immune Unconfirmed Progressive Disease (iUPD)	Requires $\geq 20\%$ and a ≥ 5 mm increase in the sum of measures of target lesions, taking as reference the nadir time point The nadir time point is the time point with the smallest target lesion sum on study, including pre RECIST 1.1 PD time points
Immune Stable Disease (iSD)	When the requirements for iCR or iPR are not met, in the absence of iUPD
Immune Confirmed Progressive Disease (iCPD)	A target lesion assessment of iCPD requires worsening of target lesions as evidenced by an increase of ≥ 5 mm in the target lesion SOM with reference to an immediately prior target lesion assessment of iUPD.

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Non-target Lesion Assessments

The table within this section defines non-target lesion assessments per iRECIST.

Table 11-9. iRECIST Non-target Assessments

iRECIST Non-Target Lesion Assessments	Requirements
Immune Complete response (iCR)	Requires disappearance of all non-nodal non-target lesions and normalization of pathological non-target lymph nodes to < 10 mm in short axis
Immune Unconfirmed Progressive Disease (iUPD)	Requires unequivocal progression of non-target lesions
Non-iCR/non-iUPD	Requires persistence of one or more non-target lesions and not meeting the non-target lesion requirements for iCR or iPD
Immune Confirmed Progressive Disease (iCPD)	Requires worsening of non-target lesions in comparison to an immediately prior non-target lesion assessment of iUPD.

New Lesions

New lesions that meet the RECIST 1.1 definition of a target lesion (non-nodal ≥ 10 mm in longest diameter or nodal ≥ 15 mm in the short axis) are categorized as new target lesions. iRECIST recommends measuring up to five new target lesions and that other new lesions are categorized as new non-target lesions (nodal lesions must be ≥ 10 mm in short axis to be considered pathological).

A separate sum, the SOM of new lesions, is calculated by taking the sum of new target lesion measurements. After first appearance, new lesions can worsen, remain unchanged, or disappear. If the SOM of new target lesions increases by ≥ 5 mm, there is unequivocal worsening of new non-target lesions, or appearance of additional new lesions this is considered worsening. Otherwise, the persistence of new lesions is considered unchanged.

Overall Response

The first table within this section defines overall response assessments per iRECIST. The second table provides further detail on confirmation of progressive disease ie, the assessment of iCPD.

Table 11-10. iRECIST Overall Response

iRECIST Target Lesion Assessments	Requirements
Immune Complete Response (iCR)	• Can only be assessed after the initial iRECIST iUPD time point (ie, the time point of RECIST 1.1 PD) • Requires <u>all</u> of the following: • Disappearance of all non-nodal target lesions and normalization of pathological target lymph nodes to < 10 mm in short axis – if any were present • Disappearance of all non-nodal non-target lesions and normalization of pathological non-target lymph nodes to < 10 mm in short axis - if any were present • No new lesions can appear for the first time or persist. Any previously identified new lesions must have disappeared.
Immune Partial Response (iPR)	• Can only be assessed after the initial iRECIST iUPD time point (ie, the time point of RECIST 1.1 PD) • Requires <u>all</u> of the following: • ≥ 30% decrease in sum of measures of target lesions with reference to the baseline target lesion sum ▪ The reference time point is the subject's original baseline time point acquired prior to drug initiation • Non-target persistence without worsening or non-target complete resolution • No new lesions can appear for the first time. No worsening of new lesions. Persistent new lesions can be present if unchanged.
Immune Unconfirmed Progressive Disease (iUPD)	• Always assessed at the time point of RECIST 1.1 PD (ie, the initial iRECIST iUPD time point), can also be assessed after RECIST 1.1 PD • Requires <u>any</u> of the following: • ≥ 20% and a ≥ 5 mm increase in the sum of measures of target lesions, with reference to nadir time point (ie, the time point with the smallest target lesion sum on study) ▪ The reference time point is the time point with the smallest target sum since (and including) the original baseline • Unequivocal progression of non-target lesions • First appearance of new lesions
Immune Stable Disease (iSD)	• Can only be assessed after the initial iRECIST iUPD time point (ie, the time point of RECIST 1.1 PD) • Is assessed when the requirements for iCR or iPR are not met, in the absence of iUPD
Immune Confirmed Progressive Disease (iCPD)	See Table 11-11

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Table 11-11. iCPD Requirements Summary

Immune Confirmed Progressive Disease (iCPD) Requirements	
An overall response of iCPD can <u>only</u> be assessed immediately after a time point with overall response of iUPD ¹	
Cause of iUPD	iCPD Requirements
Target Lesion Progression	Additional worsening of target lesions as evidenced by an increase of ≥ 5 mm in the target lesion SOM
Non-Target Lesion Progression	Any worsening in non-target lesions
New Target Lesions	Additional worsening of new target lesions as evidenced by an increase of ≥ 5 mm in the new target lesion SOM, or additional new target lesions
New Non-Target Lesions	Any worsening in non-target new lesion lesions or additional non-target new lesions
Any cause	New RECIST 1.1-assigned progression in another lesion category (ie, target or non-target lesions reach the definition of iUPD for the first time per Table 11-8 or Table 11-9 , or there are new lesions for the first time)

¹ Or immediately after an assessment of UE, NA, or ND if the assessment immediately before was iUPD

- Unable to evaluate (UE): Any lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point
- Not Available (NA): Scan not available
- Not Done (ND): Radiographic imaging was not performed at this time point to evaluate the target lesions

Best Overall Response

Immune Best Overall Response (iBOR) is determined for iBOR as follows:

- iBOR is the best response seen since iUPD
- iBOR does not require confirmation
- For an iBOR of progression, the time point of iUPD that turned into iCPD is the time point of iBOR

Special Cases

Bone lesions, cystic lesions, lesions with prior treatment, fluid collections, merging lesions, and splitting lesions are given special mention within the RECIST 1.1 publication. These considerations should also be applied to iRECIST.

Methods of Assessment and Image Acquisition Specifications

For each subject at each timepoint, there is a separate RECIST 1.1 assessment and iRECIST assessment. Until PD has been reached, these assessments rely on the same measurements and NT/new lesion assessments. Subsequently, the assessments will differ as described above. Image acquisition for a subject should be kept consistent for the entire time the subject is on trial, including for the post RECIST 1.1 PD time points, which are assessed by iRECIST.

11.13 Appendix 13. Symptoms Review Questionnaire

The questions below should be provided to all subjects who receive treatment with AMG 256.

Subjects are to be instructed to review the questions routinely and notify the treating investigator immediately if any of the below symptoms are noted.

- Do you have any new, unusual or unexplained:
 - Swelling in the mouth or throat area?
 - Difficulty with breathing?
 - Bruise-like marks?
 - Bleeding from blood draws or cuts on the skin (ie, shaving)?
 - Small red or purple dots on the skin, inside the mouth or gums?
 - Bleeding while brushing your teeth?
 - Nose bleeds?
 - Blood in the urine, dark or tarry stools, or fresh blood in the toilet after use?
- Do you have any other new side effects of concern?

Approved

Protocol Title: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 256 in Patients With Advanced Solid Tumors

Amgen Protocol Number 20180144

IND Number 144008

EudraCT number

Amendment Date: 20 March 2020

Rationale:

The protocol has been revised based on FDA review to:

- Include a new starting dose cohort at ■■■ mg, expected to result in C_{max} exposures closer to the EC₅₀. The dose escalation has been adjusted accordingly.
- Provided clarification throughout that late onset immune-mediated toxicities will be reviewed during dose level review meetings (DLRMs).

Additional changes have been made to:

- Correct safety adverse event collection time frame,
- Add phosphate and uric acid collection to analytes for a more comprehensive information of chemistries,
- Increase monitoring frequency of pituitary function (ACTH collected prior to every cycle not every other cycle),
- Provide a window to procedures in the schedule of assessments, and
- To make minor clarifications, grammatical and typographical corrections throughout.

The version number and date on all documents was updated.

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Description of Changes:

Section: Global

Replace:

The version is updated to **20 March 2020**.

Replace:

Throughout the protocol, reference to Cohorts 5-8 replaced with **Cohorts 6-9** due to renumbering of cohorts with the addition of the new starting dose cohort.

Add:

Late-onset immune-mediated toxicities added to all sections referencing information that will be reviewed during the DLRM.

Section: 1.1 Protocol Synopsis, Dose Escalation – Part 1

Section: 4.1 Overall Design, Dose Escalation – Part 1

Add and Delete:

Dose escalation will begin with single subject cohorts treated at the lowest planned dose level of [REDACTED] mg [REDACTED]

Section: 1.1 Protocol Synopsis, Summary of Subject Eligibility Criteria

Add and Delete:

Subjects enrolled to Part 2 (Dose Expansion) must have been treated with an anti-PD(L)-1 agent **and/or CTLA-4**. ~~other checkpoint inhibitor.~~

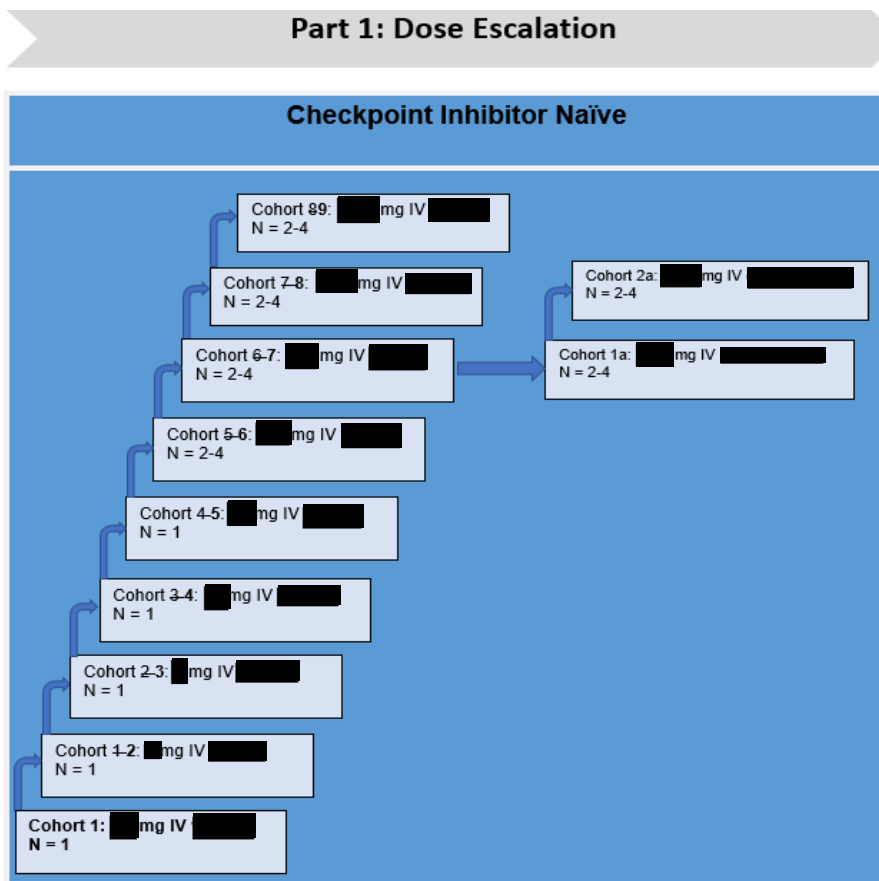
Section: 1.1 Protocol Synopsis, Treatments

Add and Delete:

AMG 256 solution for intravenous infusion will be prepared for IV infusion and delivered through infusion lines using a syringe pump (Cohorts 1-~~3~~ and 2) and preprogrammed infusion pumps (Cohorts ~~4~~ 3 and above) approved for use in the country in which the subject is undergoing treatment.

Section: 1.2 Study Schema, Figure 1-1. Study Schema

Add and Delete:



- AMG 256 will be administered IV [redacted] and [redacted] as shown with the planned cohorts for [redacted] (Cohorts 1-98) and [redacted] (Cohorts 1a and 2a) dosing.
- Dose escalation will begin with single subject cohorts treated at the lowest planned dose level with [redacted] dosing of AMG 256. The cohort size will be increased to N = 2-4 subjects after observation of treatment-related adverse events of grade 2 or higher; or escalation has reached Cohort 65; or is recommended by the DLRT to further evaluate a cohort.

Section: 1.3 Schedule of Activities (SoA), Table 1-1 Schedule of Activities – [REDACTED]

[REDACTED] Dosing and Footnotes

Add and Delete:

CYCLES
WEEKS
DAYS
Hours (relative to end of infusion)
Coagulation ^{5, 19}
Hematology ¹⁹
Chemistry ^{6,19}
[REDACTED]

² Cycle 1, Day 1: EOI and 24 (± 1) hours after EOI;

³ Evaluation of vital signs and pulse oximetry is required at the following time points:

- Screening
- During escalation:

Cycle 1, Days [REDACTED] predose, every 15 (± 5) minutes during the infusion at EOI, every 15 (± 5) minutes for the first 2 hours after EOI; every 30 (± 10) minutes 2-4 hours after EOI; every hour (± 15 minutes) 4-8 hours after EOI; every 4 hours (± 30 minutes) 8-24 hours after EOI

Cycle 2, Days [REDACTED]: predose, every 15 (± 5) minutes during infusion, at EOI, every 30 minutes (± 10) for the first 4 hours after EOI; every hour (± 15 minutes) 4-6 hours after EOI; every 6 hours (± 30 minutes) 6-24 hours after EOI

Cycle 3 and all subsequent cycles, days [REDACTED]: predose, every 15 (± 5) minutes during infusion, EOI, one hour (± 15 minutes) after EOI
- During expansion:

Cycle 1, Days [REDACTED] predose, every 15 (± 5) minutes during the infusion at EOI, every 30 (± 10) minutes for the first 4 hours after EOI; every hour (± 15 minutes) 4-6 hours after EOI

Cycle 2 and all subsequent cycles, days [REDACTED]: predose, every 15 (± 5) minutes during infusion, EOI, one hour (± 15 minutes) after EOI

~~—Note: Vitals and pulse oximetry should be taken as close to the exact nominal time point as noted above.~~

⁶ Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN/Total urea, Calcium, Chloride, Creatinine, Direct Bilirubin, Glucose, LDH, Magnesium, **Phosphate**, Potassium, Sodium, Total Bilirubin, Total protein, TSH, Free T4, **Uric Acid**

⁷ ACTH to be evaluated at screening **and prior to AMG 256 administration on day 1 of every cycle.** ~~prior to cycle 1 and then every 8 weeks.~~ ANA and ANCA to be evaluated at screening and then if clinically indicated.

¹⁸ Long term follow-up (LTFU) phone call will be done 6 months (± 1 week) after the last dose to collect information on ~~serious adverse events (Section 8.2.5.1); concomitant medications to treat SAEs,~~ start of new therapies, and disease status.

Section: 1.3 Schedule of Activities (SoA), Table 1-2 Schedule of Activities – Once [REDACTED] Dosing and Footnotes

Delete:

CYCLES WEEKS DAYS Hours (relative to end of infusion)	Screening (up to 28 days before day 1)							
		1						
		1						
		Pre-dose	0	EOI	2	6	1	
Coagulation ^{5,18}	X ⁵	X ⁵		X ⁵				
Hematology ¹⁸	X	X		X				
Chemistry ^{6,18}	X ⁶	X ⁶		X ⁶				

² Cycle 1, Day 1: EOI and 24 (± 1) hours after EOI;

³ Evaluation of vital signs and pulse oximetry is required at the following time points:

- Screening
- During escalation:
 - Cycle 1, [REDACTED]: predose, every 15 (± 5) minutes during the infusion at EOI, every 15 (± 5) minutes for the first 2 hours after EOI; every 30 (± 10) minutes 2-4 hours after EOI; every hour (± 15 minutes) 4-8 hours after EOI; every 4 hours (± 30 minutes) 8-24 hours after EOI
 - Cycle 1, [REDACTED]**
 - Cycle 2, [REDACTED] predose, every 15 (± 5) minutes during infusion, at EOI, every 30 (± 10) minutes for the first 4 hours after EOI; every hour (± 15 minutes) 4-6 hours after EOI; every 6 hours (± 30 minutes) 6-24 hours after EOI
 - Cycle 3 and all subsequent cycles, [REDACTED]: predose, every 15 (± 5) minutes during infusion, EOI, one hour (± 15 minutes) after EOI
- During expansion:
 - Cycle 1, [REDACTED]: predose, every 15 (± 5) minutes during the infusion at EOI, every 30 (± 10) minutes for the first 4 hours after EOI; every hour (± 15 minutes) 4-6 hours after EOI
 - ~~Note: Vitals and pulse oximetry should be taken as close to the exact nominal time point as possible above.~~
 - Cycle 1, [REDACTED]**
 - Cycle 2 and all subsequent cycles, [REDACTED]: predose, every 15 minutes during infusion, EOI, one hour after EOI
 - ~~Note: Vitals and pulse oximetry should be taken as close to the exact nominal time point as noted above.~~

⁶ Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN/Total urea, Calcium, Chloride, Creatinine, Direct Bilirubin, Glucose, LDH, Magnesium, **Phosphate**, Potassium, Sodium, Total Bilirubin, Total protein, TSH, Free T4, **Uric Acid**

⁷ ACTH to be evaluated at screening **and pre-dose each AMG 256 administration.**
~~prior to cycle 1 and then every 8 weeks.~~ ANA and ANCA to be evaluated at screening and then if clinically indicated.

¹² AMG 256 will be administered by intravenous infusion on [REDACTED] [REDACTED] cycle. AMG 256 should be administered on the scheduled day ± 1 day. See Table 6-1 for infusion times.

¹⁶ ADA/Immunogenicity samples will be collected predose (**on days AMG 256 is administered**) at the timepoints below. Note: Pre-dose ADA/immunogenicity samples must be collected day of dosing, within 60 minutes prior to the AMG 256 infusion.

¹⁸ Long term follow-up (LTFU) phone call will be done 6 months ($\pm$ 1 week) after the last dose to collect information on ~~serious adverse events (Section 8.2.5.1); concomitant medications to treat SAEs, start of new therapies, and disease status.~~

Section: 4.3 Justification for Investigational Dose

Add and Delete:

The proposed doses of AMG 256 for the FIH study are [REDACTED] and [REDACTED] mg [REDACTED] and [REDACTED] and [REDACTED] mg [REDACTED] as short-term IV infusions (planned durations of [REDACTED] for the first 2 cycles of treatment [first 8 [REDACTED] or 4 [REDACTED] doses], [REDACTED] for the 3rd cycle [9th to 12th [REDACTED] or 5th and 6th [REDACTED] doses], and [REDACTED] thereafter) in subjects with advanced solid tumors.

The AMG 256 starting dose was based on the [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (Saber et al, 2016).

Furthermore, relative to the use of 1/6th of the highest non-severely toxic dose (HNSTD) of [REDACTED] mg/kg in cynomolgus monkeys as the basis for defining the starting dose for anti-cancer drugs (ICH S9, 2009), a [REDACTED] mg dose remains a more conservative approach. This approach is also supported by the calculation of the expected human exposure multiples, which were approximately 1339 [REDACTED] and 6878 [REDACTED]-fold for AUC and C_{max}, respectively, at a starting dose of [REDACTED]-mg relative to the HNSTD of [REDACTED] mg/kg.

Section: 6.1.1 Investigational Products, Table 6-1 Study Treatments

Add and Delete:

Route of Administration	AMG 256 solution for infusion will be prepared for IV infusion and delivered through infusion lines using a syringe pump (Cohorts 1-3 and 2) and a preprogrammed infusion pump (Cohorts 4 3 and higher) approved for use in the country in which the subject is undergoing treatment.
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Dosing Instructions	For multi-subject cohorts in dose escalation, sites must receive written confirmation from the study team prior to all doses during cycles 1 and 2 with approval that it is safe to proceed with dosing. ~~Sites must notify the study team when a subject has been dosed and if subject experienced any significant adverse reaction (ie, infusion-related reaction or hypersensitivity reaction).~~ During cycles 1 and 2 for multi-subject cohorts in dose escalation, sites must notify the study team when a subject has been dosed and if subject experienced any significant adverse reaction(s) (ie, infusion-related reaction or hypersensitivity reaction).
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Section: 8.2.5.1.2 Serious Adverse Events

Add and Delete:

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 the **safety follow-up (90 ± 7] days after last dose of AMG 256) visit** ~~end of study~~ are reported using the Event CRF.

Section: 9.4.1.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules, Dose Cohort Stopping Rules

Add and Delete:

Key details of the BLRM model as used in this study are as follows. A bi-variate normal prior distribution (parameters “a” and “b”) is used for the BLRM model with bi-variate normal prior are as follows: the mean natural log (ln) of “a” $\ln(a) = -0.847$, standard deviation (SD) of “a” $SD(a) = 1.275$, mean $\ln(b) = -0.727$ ~~-0.611~~ $SD(b) = 3.269$ and correlation = 0. The prior distribution is specified such that probability of dose-limiting toxicity (DLT) is [REDACTED] for the starting dose ([REDACTED]-mg) and [REDACTED] for the reference dose ([REDACTED] mg), where the probability that the true DLT rate is ≤ 0.40 at the lowest planned dose is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose is 0.05.

Section: 11.2, Appendix 2. Clinical Laboratory Tests, Table 11-1. Analyte Listing

Add:

Local Laboratory: Chemistry
Sodium
Potassium
Chloride
Bicarbonate
Total protein
Albumin
Calcium
Adjusted calcium
Magnesium
Phosphate
Glucose
BUN or Urea
Creatinine
Total bilirubin
Direct bilirubin
ALP
LDH
AST (SGOT)
ALT (SGPT)
TSH
Free T4
Uric Acid