Title Page

Protocol Title:		A Phase 1, Multicenter, Open-label, Dose Exploration and Dose Expansion Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 994 Monotherapy and Combination of AMG 994 and AMG 404 in Subjects with Advanced Solid Tumors
Short Protocol Title:		AMG 994 Monotherapy and AMG 994 and AMG 404 Combination Therapy in Patients with Advanced Solid Tumors
Protocol Number:		20190136
Investigational Product:		AMG 994 and AMG 404
Sponsor	**Name of Sponsor:**	Amgen
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EudraCT Number:		2020-003937-40
NCT Number:		**NCT04727554**
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Data Elements Standards Version:		6.0

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

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 1, Multicenter, Open-label, Dose Exploration and Dose Expansion Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 994 Monotherapy and Combination of AMG 994 and AMG 404 in Subjects with Advanced Solid Tumors, dated **16 June 2022**, and agree to abide by all provisions set forth therein.

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

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

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

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1, Multicenter, Open-label, Dose Exploration and Dose Expansion Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 994 Monotherapy and Combination of AMG 994 and AMG 404 in Subjects with Advanced Solid Tumors

Short Protocol Title: AMG 994 Monotherapy and AMG 994 and AMG 404 Combination Therapy in Patients with Advanced Solid Tumors

Study Phase: 1
Indication: Advanced solid tumors
Rationale

AMG 994 is a bivalent bispecific monoclonal immunoglobulin G1 (IgG1) stable effector functionless (SEFL2) directed against mesothelin (MSLN) and clusters of differentiation 40 (CD40) and AMG 404 is a fully human, monoclonal IgG1 SEFL2 directed against programmed cell death protein 1 (PD-1) currently being evaluated by Amgen. Nonclinical studies with an AMG 994 mouse surrogate alone showed a dose-dependent reduction in tumor growth and improvement in overall survival compared with treatment with an isotype control antibody, while the combination of the AMG 994 mouse surrogate plus an anti programmed death ligand 1 (PD-L1) molecule promoted increased complete tumor regression relative to either individual treatment alone. A recent review by Vonderheide (2020) of clinical experience with CD40 agonist antibodies suggests limited monotherapy efficacy, but the potential to show increased efficacy in combination with other immunotherapies, such as PD-1 blockade.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the safety, tolerability, and maximum tolerated dose (MTD)/maximum tolerated combination dose (MTCD) or recommended phase 2 dose (RP2D) of AMG 994 as monotherapy and AMG 994 in combination with AMG 404 in subjects with advanced solid tumors	• Dose-limiting toxicities (DLTs) • Treatment-emergent and treatment related adverse events (including all adverse events, grade ≥ 3, serious adverse events, fatal adverse events, adverse events requiring permanent discontinuation of study treatment, and immune-related events)

	• Changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
Secondary	
• Preliminary evaluation of anti-tumor activity of AMG 994 as monotherapy and AMG 994 in combination with AMG 404	• Objective response (OR) per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • Duration of response (per modified RECIST 1.1) • Overall survival (OS) • Progression-free survival (per modified RECIST 1.1) • Time to progression (per modified RECIST 1.1) • Time to subsequent therapy
• Characterize the PK of AMG 994 monotherapy and AMG 994 in combination with AMG 404	PK parameters • Maximum serum concentration (C_{max}) • Minimum serum concentration (C_{min}) • Area under the concentration-time curve (AUC) over the dosing interval • Half-life ($t_{1/2}$), if feasible

Overall Design

This is a First In Human (FIH), multicenter, non-randomized, open-label, phase 1 study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary efficacy of AMG 994 monotherapy and evaluation of AMG 994 in combination with AMG 404 in subjects with advanced solid tumors with known MSLN expression, including mesothelioma, non-small cell lung cancer (NSCLC) squamous cell carcinoma [Part 2 only] and adenocarcinoma [Part 1 and Part 2], pancreatic adenocarcinoma, and high grade serous ovarian carcinoma (platinum resistant). Study assessments will include measures of safety, tolerability, PK, and pharmacodynamics data, and preliminary anti-tumor activity.

AMG 994 will be administered by [redacted] and AMG 404 will be administered by [redacted] The study will be conducted in 2 parts: Part 1 – Dose Exploration and Part 2 – Dose Expansion.

Part 1 is aimed at evaluating the safety, tolerability, PK, and pharmacodynamics of AMG 994 monotherapy and AMG 994 in combination with AMG 404 using sequential and concurrent initiation of dosing:

The maximum tolerated dose/maximum tolerated combination dose (MTD/MTCD) of the combination in subjects with advanced solid tumors will be determined using a Bayesian Logistics Regression Model (BLRM) design. Part 2 will further evaluate the safety of the MTD/MTCD and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) of the combination in specific tumor types. The dose expansion part of the study (Part 2) will be opened once the MTD/MTCD/RP2D of the combination has been determined in Part 1.

The dose exploration part of the study will consist of approximately 94 subjects and the dose expansion will consist of approximately 120 additional subjects, 30 subjects in each of 4 tumor types (mesothelioma, NSCLC squamous cell carcinoma and adenocarcinoma [in Part 2, if upon screening found to be MSLN positive], pancreatic adenocarcinoma, and high grade serous ovarian carcinoma). Dose escalation will be conducted in subjects with metastatic or locally advanced solid tumors of types known to express MSLN for which no standard systemic therapy exists and dose expansion will be conducted in subjects with specific tumor types. The DLT evaluation period will be [redacted] for each cycle. Administration of AMG 994 (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 subject achieves a complete response, and up to 24 months if partial response or stable disease.

Number of Subjects

Approximately 214 subjects with advanced solid tumors of types known to express MSLN will be enrolled in the study. During Dose Exploration (Part 1), screening for MSLN expression will not occur and up to 94 evaluable subjects will be enrolled. During Dose Expansion (Part 2), approximately 120 evaluable subjects, 30 subjects in each of 4 tumor types (mesothelioma, NSCLC squamous cell carcinoma and adenocarcinoma [if

upon screening are found to be MSLN positive], pancreatic adenocarcinoma, and high grade serous ovarian carcinoma) will be enrolled.

Summary of Subject Eligibility Criteria

Male or female subjects ≥ 18 years of age at the time of informed consent who have advanced solid tumors of known MSLN expression who have relapsed after and/or are refractory to established and available therapies with known clinical benefit.

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

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

Treatments

AMG 994 is supplied as a sterile, single-use, preservative-free solution for [redacted] AMG 994. [redacted] with AMG 994 doses administered [redacted] and AMG 404 doses of [redacted] administered [redacted] in subjects with advanced solid tumors. Planned AMG 994 dose levels for the dose exploration cohorts are as follows: [redacted], and [redacted] Based on emerging data and DLRM recommendation, intermediate and/or alternative dose levels and schedules (eg, dose dense) may be implemented.

AMG 404 is supplied as a sterile, single-use, preservative-free solution for [redacted] AMG 404. Taking into consideration cumulative preliminary safety, PK, pharmacodynamics, and immunogenicity data as of 14 February 2020, the AMG 404 recommended dose for evaluation in combination therapy is [redacted] in subjects with advanced solid tumors.

Procedures

Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed. Scans performed prior to consent may be used for screening provided they are accessed for study purposes after consent has been obtained. Study-specific procedures will occur according to the Schedule of Assessments (Section 1.3).

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

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

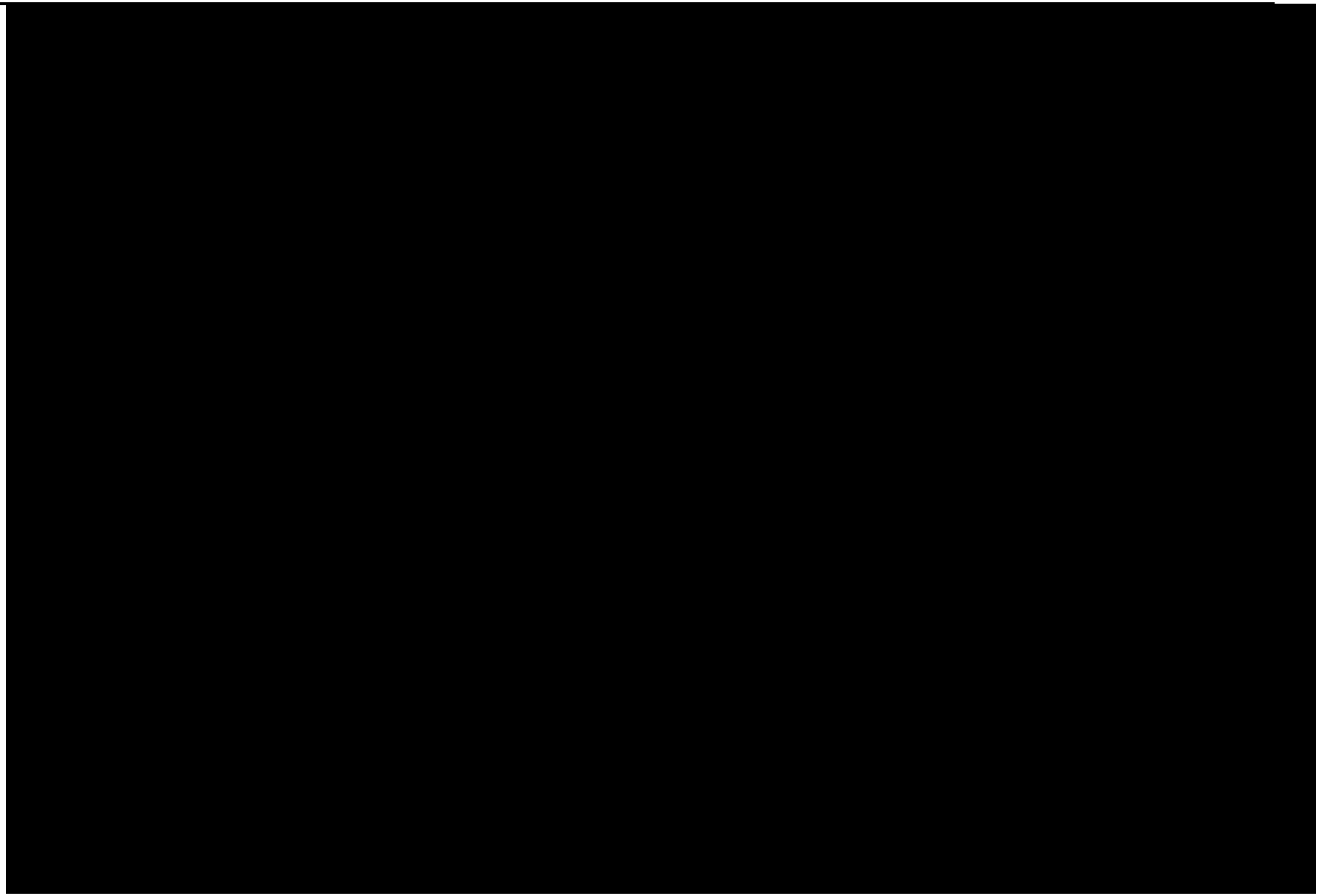
For a full description of statistical analysis methods, please refer to Section 9.

Statistical Hypotheses

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

Sponsor Name: Amgen

1.2 Study Schema



1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities: Dose Exploration AMG 994 Monotherapy Cycles

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to end of infusion)	
GENERAL AND SAFETY ASSESSMENTS	
Informed consent	X
Inclusion and exclusion criteria	X
Demographics	X
Physical examination, ECOG PS[12]	X X X X X

Footnotes defined on last page of this table

Table 1-1. Schedule of Activities: Dose Exploration AMG 994 Monotherapy Cycles

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to end of infusion)	
Medical history	
ECG triplicate measurement[1]	X X X (X) X X (X) X X (X) X X X (X) X X X
Vital signs, pulse ox[2]	X ◄——► ◄——► ◄——► ◄——►
Adverse events review	◄——————————————————————————————————►
Serious adverse events	◄——————————————————————————————————►
Concomitant medication review	◄——————————————————————————————————►

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Table 1-1. Schedule of Activities: Dose Exploration AMG 994 Monotherapy Cycles

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to end of infusion)	
LABORATORY ASSESSMENTS	
Pregnancy test (females of childbearing potential only)[3]	X X
Coagulation	X X X X X X X X
Hematology	X X X X X X X X
Chemistry[4]	X X X X X X X X

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Table 1-1. Schedule of Activities: Dose Exploration AMG 994 Monotherapy Cycles

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to end of infusion)	

HIV, Hepatitis B and C screening	X																																					
Urinalysis	X	X											X									X																	
ACTH[5]	X	X																																				
ANA, ANCA[5]	X																																					

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Table 1-1. Schedule of Activities: Dose Exploration AMG 994 Monotherapy Cycles

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to end of infusion)	
RADIOLOGICAL ASSESSMENTS	
CT/MRI and Tumor Burden Assessment [6]	X ... X
Brain MRI[6]	X
DOSING	
AMG 994[7]	X, X, X, X
Hospitalization[8]	X, X, X, X

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Table 1-1. Schedule of Activities: Dose Exploration AMG 994 Monotherapy Cycles

CYCLES	[redacted]																																							
WEEKS																																								
DAYS																																								
Hours (relative to end of infusion)																																								
PHARMACOKINETIC ASSESSMENTS AMG 994[9]		X		X		X		X	X	X	X	X	X		X							X		X							X		X		X		X	X	X	
ARCHIVAL TUMOR TISSUE[10]	X																																							
PRE-TREATMENT TISSUE/FRESH TUMOR BIOPSIES[11]	X																																							X
WHOLE BLOOD FOR CYTOMETRY	X	X						X		X			X									X									X									

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Table 1-1. Schedule of Activities: Dose Exploration AMG 994 Monotherapy Cycles

CYCLES	[redacted]																																							
WEEKS																																								
DAYS																																								
Hours (relative to end of infusion)																																								
SERUM MARKERS		X					X		X	X	X	X						X		X	X																			
PLASMA FOR ctDNA ANALYSIS	X	X										X									X																			
PBMC		X							X	X		X								X	X																			
[redacted]																																								

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(X) = conditional, refer to applicable footnote

ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; ANA = anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibodies; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOT = end of treatment; HIV = human immunodeficiency virus; [redacted] MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetics; PR = partial response; WOCBP = women of child bearing potential.

[1] ECGs are required in triplicate approximately 30 to 60 seconds apart and run consecutively for the first 3 cycles during Dose Exploration as described below for each cohort at the following time points (± 5 minutes):

- [redacted] predose, EOI (AMG 994 and AMG 404, as applicable), and 24 hours after AMG 994 EOI (during cycles where hospitalization is required).
- As clinically indicated

[redacted]

No ECGs after cycle 3 for any cohort unless clinically indicated; ECGs at 24 hours after AMG 994 infusion only required for cycles in which hospitalization is required.

[2] Vital signs, pulse ox are required at the following time points (± 5 minutes):

- Screening

During exploration:

[redacted]

During expansion:

[redacted]

Note: Vitals and pulse oximetry should be taken as close to the exact nominal time point as noted above.
Note: [redacted] during infusion timepoint is relative to AMG 994 infusion.
Note: EOI and Post-EOI timepoints for all combination cycles are relative to AMG 404 infusion.

[3] WOCBP, an initial serum pregnancy test is required prior day 1 of cycle 1; a urine pregnancy test is required at least Q4W thereafter prior to day 1 dosing of all cycles

[4] Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN/total urea, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein

[5] ACTH to be done once every cycle. ANA and ANCA to be done at screening and then if clinically indicated.

[6] Radiological imaging and tumor assessments are required at screening, cycle 1 [redacted] thereafter (C3[redacted] C5[redacted] C [redacted] and EOT [redacted] Every assessment must include the chest, abdomen, and pelvis and all other known sites of disease. Tumor burden assessments will be performed based on RECIST 1.1 guidelines (Section 11.11). Radiographic response (CR and PR) requires confirmation by a repeat assessment at least 4 weeks after the first detection of response. All subjects must have MRI of the brain performed within 28 days prior to enrollment. Only if MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain scans may be performed at any time if subject has history of CNS disease or as clinically indicated. Any supplemental imaging used to evaluate or determine response by sites should be sent along with the required scans to the central imaging vendor promptly upon completion.

[7] AMG 994 will be administered [redacted]

[8] Subjects will be hospitalized for a minimum of 24 hours following each infusion during the first cycle of treatment on study and following the week 1 infusion of the second cycle of treatment on study. Hospitalization should be extended if any adverse event, clinical change, or safety concern associated with the infusion is observed. This will be based on investigator and Amgen Medical Monitor discretion. Subjects will be observed for 6 hours following each remaining infusion (weeks 2, 3, and 4) during the second cycle of treatment on study and observed for 2 to 4 hours following each subsequent infusion for observation of any side effects.

[9] PK blood samples should be collected at the exact nominal time point as noted above [see hours (relative to end of infusion) row]. If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations.

[10] If available, archived tumor tissue (archival within < 6 months of enrollment**)** or recent acquisition will be collected prior to cycle 1, day 1 (during screening).
[11] A tumor biopsy is required at baseline if patient has received any pre-treatment prior to participating in this study. Tumor tissue must be available for correlative studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or unstained slides) by study personnel for performance of correlative tissue studies. Fresh tumor biopsies are required for subsequent time points. [redacted]

[12] Physical exam is required on days [redacted] of each cycle. Height will be measured at screening only. Weight will be measured at screening and each study visit where a physical exam is also performed.

[redacted]

Table 1-2. Schedule of Activities: Dose Exploration for First Cycle of AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]																																								
WEEKS																																									
DAYS																																									
Hours (relative to AMG 994 end of infusion)																																									
Hours (relative to AMG 404 end of infusion)																																									
GENERAL AND SAFETY ASSESSMENTS																																									
Informed consent	X																																								
Inclusion and exclusion criteria	X																																								
Demographics	X																																								
Physical examination, ECOG PS[14]	X	X												X									X									X									
Medical history	X																																								

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Table 1-2. Schedule of Activities: Dose Exploration for First Cycle of AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]																																									
WEEKS																																										
DAYS																																										
Hours (relative to AMG 994 end of infusion)																																										
Hours (relative to AMG 404 end of infusion)																																										
ECG triplicate measurement[1]	X	X		X			X					(X)			X		X						(X)	X		X						(X)	X		X						X	
Vital signs, pulse ox[2]	X	←→													←→									←→									←→									
Adverse events review				←→																																						
Serious adverse events		←→																																								
Concomitant medication review		←→																																								

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Table 1-2. Schedule of Activities: Dose Exploration for First Cycle of AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]																																									
WEEKS																																										
DAYS																																										
Hours (relative to AMG 994 end of infusion)																																										
Hours (relative to AMG 404 end of infusion)																																										
LABORATORY ASSESSMENTS																																										
Pregnancy test (females of childbearing potential only)[3]	X	X																																								
Coagulation	X	X					X					X			X		X						X	X		X						X	X		X						X	
Hematology	X	X					X					X			X		X						X	X		X						X	X		X						X	

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Table 1-2. Schedule of Activities: Dose Exploration for First Cycle of AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]																																								
WEEKS																																									
DAYS																																									
Hours (relative to AMG 994 end of infusion)																																									
Hours (relative to AMG 404 end of infusion)																																									
Chemistry[4]	X	X					X					X			X		X						X	X		X						X	X		X						X	
HIV, Hepatitis B and C screening	X																																									
Urinalysis	X	X													X									X									X									
ACTH[5]	X	X																																								
ANA, ANCA[5]	X																																									

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Table 1-2. Schedule of Activities: Dose Exploration for First Cycle of AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]																																									
WEEKS																																										
DAYS																																										
Hours (relative to AMG 994 end of infusion)																																										
Hours (relative to AMG 404 end of infusion)																																										
RADIOLOGICAL ASSESSMENTS																																										
CT/MRI and Tumor Burden Assessment[6]	X																																									X
Brain MRI[6]	X																																									
DOSING																																										
AMG 994[7]			X													X									X									X								
AMG 404[13]						X																																				
Hospitalization[8]		X													X																		X									

Footnotes defined on last page of this table

Table 1-2. Schedule of Activities: Dose Exploration for First Cycle of AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]																																									
WEEKS																																										
DAYS																																										
Hours (relative to AMG 994 end of infusion)																																										
Hours (relative to AMG 404 end of infusion)																																										
PHARMACOKINETIC ASSESSMENTS AMG 994[9]		X		X		X			X	X	X	X	X	X	X		X							X		X							X		X				X	X	X	
PHARMACOKINETIC ASSESSMENTS AMG 404[9]		X					X		X	X	X	X	X	X	X									X									X									
ARCHIVAL TUMOR TISSUE[10]	X[10]																																									

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Table 1-2. Schedule of Activities: Dose Exploration for First Cycle of AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]																																								
WEEKS																																										
DAYS																																									
Hours (relative to AMG 994 end of infusion)																																									
Hours (relative to AMG 404 end of infusion)																																									
PRE-TREATMENT TISSUE/FRESH TUMOR BIOPSIES[11]	X																																								X
WHOLE BLOOD FOR CYTOMETRY	X	X								X		X			X										X									X								
SERUM MARKERS		X								X		X	X	X	X							X		X	X								X		X	X						
PLASMA FOR ctDNA ANALYSIS	X	X													X									X										X								

Footnotes defined on last page of this table

Table 1-2. Schedule of Activities: Dose Exploration for First Cycle of AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
PBMC	X X X X X X X X
[redacted]	

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(X) = conditional, refer to applicable footnote

ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; ANA = anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibodies; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; HIV = human immunodeficiency virus; [redacted] MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic(s); PR = partial response; WOCBP = women of child bearing potential.

[1] ECGs are required in triplicate approximately 30 to 60 seconds apart and run consecutively for the first 3 cycles during Dose Exploration as described below for each cohort at the following time points (± 5 minutes):

- Days [redacted]: predose, EOI (AMG 994 and AMG 404, as applicable), and 24 hours after AMG 994 EOI (during cycles where hospitalization is required).
- As clinically indicated

[redacted]

No ECGs after cycle 3 for any cohort unless clinically indicated; ECGs at 24 hours after AMG 994 infusion only required for cycles in which hospitalization is required.

[2] Evaluation of vital signs and pulse oximetry is required at the following time points (± 5 minutes):

- Screening

During exploration:

[redacted]

During expansion:

[redacted]

Note: Vitals and pulse oximetry should be taken as close to the exact nominal time point as noted above.
Note: [redacted] during infusion timepoint is relative to AMG 994 infusion.
Note: EOI and Post-EOI timepoints for all combination cycles are relative to AMG 404 infusion.

[3] WOCBP, an initial serum pregnancy test is required prior day 1 of cycle 1; a urine pregnancy test is required at least Q4W thereafter prior to day 1 dosing

[4] Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN/total urea, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein

[5] ACTH to be done once every cycle. ANA and ANCA to be done at screening and then if clinically indicated.

[6] Radiological imaging and tumor assessments are required at screening, cycle 1 [redacted] Every assessment must include the chest, abdomen, and pelvis and all other known sites of disease. Tumor burden assessments will be performed based on RECIST 1.1 guidelines (Section 11.11). Radiographic response (CR and PR) requires confirmation by a repeat assessment at least 4 weeks after the first detection of response. All subjects must have MRI of the brain performed within [redacted] prior to enrollment. Only if MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain scans may be performed at any time if subject has history of CNS disease or as clinically indicated. Any supplemental imaging used to evaluate or determine response by sites should be sent along with the required scans to the central imaging vendor promptly upon completion.

[7] AMG 994 will be administered [redacted]

[8] Subjects will be hospitalized for a minimum of 24 hours following each infusion during the first cycle of treatment on study and following the week 1 infusion of the second cycle of treatment on study. Hospitalization should be extended if any adverse event, clinical change, or safety concern associated with the infusion is observed. This will be based on investigator and Amgen Medical Monitor discretion. Subjects will be observed for 6 hours following each remaining infusion (weeks 2, 3, and 4) during the second cycle of treatment on study and observed for 2 to 4 hours following each subsequent infusion for observation of any side effects.

[9] PK blood samples for AMG 994 and AMG 404 should be collected at the exact nominal time point relative to their respective end of infusions as noted above [see hours (relative to end of infusion) rows for AMG 994 and AMG 404]. If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations.

[10] If available, archived tumor tissue (archival within < 6 months of enrollment) or recent acquisition will be collected prior to cycle 1, day 1 (during screening).

[11] A tumor biopsy is required at baseline. Tumor tissue (archival within < 6 months of enrollment or recent acquisition) must be available for correlative studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or unstained slides) by study personnel for performance of correlative tissue studies. Fresh tumor biopsies are required for subsequent time points. [redacted] tumor biopsy sample during combination therapy is only required for subjects on their first cycle of treatment [redacted]

[redacted] AMG 404 to be administered on [redacted] fter the end of infusion of AMG 994 if a ≥ grade 2 infusion reaction is not observed. The dose is [redacted]

[14] Physical exam is required on days [redacted] of each cycle. Height will be measured at screening only. Weight will be measured at screening and each study visit where a physical exam is also performed.

Table 1-3. Schedule of Activities: Dose Exploration AMG 994 and AMG 404 Second Combination Therapy Cycle and Beyond

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
GENERAL AND SAFETY ASSESSMENTS	
Informed consent	
Inclusion and exclusion criteria	
Demographics	

Footnotes defined on last page of this table

Table 1-3. Schedule of Activities: Dose Exploration AMG 994 and AMG 404 Second Combination Therapy Cycle and Beyond

CYCLES	[redacted]																																						
WEEKS																																							
DAYS																																							
Hours (relative to AMG 994 end of infusion)																																							
Hours (relative to AMG 404 end of infusion)																																							
Physical examination, ECOG PS[13]	X									X								X										X									X	X	
Medical history																																							
ECG triplicate measurement[1]	X		X		X				(X)	X		X						(X)		(X)			(X)					(X)		(X)									

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Footnotes defined on last page of this table

Table 1-3. Schedule of Activities: Dose Exploration AMG 994 and AMG 404 Second Combination Therapy Cycle and Beyond

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
Vital signs, pulse ox[2]	
Adverse events review	
Serious adverse events	

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Footnotes defined on last page of this table

Table 1-3. Schedule of Activities: Dose Exploration AMG 994 and AMG 404 Second Combination Therapy Cycle and Beyond

CYCLES	[redacted]																																					
WEEKS																																						
DAYS																																						
Hours (relative to AMG 994 end of infusion)																																						
Hours (relative to AMG 404 end of infusion)																																						
Concomitant medication review	←→																																					
LABORATORY ASSESSMENTS																																						
Pregnancy test (females of childbearing potential only)[3]	X																	X																		X	X	
Coagulation	X				X					X		X						X				X					X		X							X	X	

Footnotes defined on last page of this table

Table 1-3. Schedule of Activities: Dose Exploration AMG 994 and AMG 404 Second Combination Therapy Cycle and Beyond

CYCLES	[redacted]																																						
WEEKS																																							
DAYS																																							
Hours (relative to AMG 994 end of infusion)																																							
Hours (relative to AMG 404 end of infusion)																																							
Hematology	X				X					X		X						X					X					X		X							X	X	
Chemistry[4]	X				X					X		X						X					X					X		X							X	X	
Urinalysis	X									X								X										X									X	X	
ACTH[5]	X																	X																					
ANA, ANCA[5]																																							

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Footnotes defined on last page of this table

Table 1-3. Schedule of Activities: Dose Exploration AMG 994 and AMG 404 Second Combination Therapy Cycle and Beyond

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
RADIOLOGICAL ASSESSMENTS	
CT/MRI and Tumor Burden Assessment[6]	X
Brain MRI[6]	X

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Footnotes defined on last page of this table

Table 1-3. Schedule of Activities: Dose Exploration AMG 994 and AMG 404 Second Combination Therapy Cycle and Beyond

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
DOSING	
AMG 994[7]	X X X X
AMG 404[15]	X X
Hospitalization/ Observation[8]	(X) (X) (X) (X)

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Table 1-3. Schedule of Activities: Dose Exploration AMG 994 and AMG 404 Second Combination Therapy Cycle and Beyond

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
PHARMACOKINETIC ASSESSMENTS – AMG 994[9]	X X X X X X X X (X) X X X X
PHARMACOKINETIC ASSESSMENTS – AMG 404[9]	X X X (X) X X
PRE-TREATMENT TISSUE/FRESH TUMOR BIOPSIES[10]	

Footnotes defined on last page of this table

Table 1-3. Schedule of Activities: Dose Exploration AMG 994 and AMG 404 Second Combination Therapy Cycle and Beyond

CYCLES	[redacted]																																					
WEEKS																																						
DAYS																																						
Hours (relative to AMG 994 end of infusion)																																						
Hours (relative to AMG 404 end of infusion)																																						
WHOLE BLOOD FOR CYTOMETRY	X									X								X									X											
SERUM MARKERS	X						X											X									X									X		
PLASMA FOR ctDNA ANALYSIS	X																	X									X									X		
PBMC	X																	X									X									X		

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Table 1-3. Schedule of Activities: Dose Exploration AMG 994 and AMG 404 Second Combination Therapy Cycle and Beyond

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
Phone Call	X

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(X) = conditional, refer to applicable footnote

ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; ANA = anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibodies; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOT = end of treatment; HIV = human immunodeficiency virus; [redacted] LTFU = long-term follow-up; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic(s); PR = partial response; SFU = safety follow-up; WOCBP = women of child bearing potential.

[1] ECGs are required in triplicate approximately 30 to 60 seconds apart and run consecutively for the first 3 cycles during Dose Exploration as described below for each cohort at the following time points (± 5 minutes):

- Days [redacted]: predose, EOI (AMG 994 and AMG 404, as applicable), and 24 hours after AMG 994 EOI (during cycles where hospitalization is required).
- As clinically indicated

[redacted]

No ECGs after cycle 3 for any cohort unless clinically indicated; ECGs at 24 hours after AMG 994 infusion only required for cycles in which hospitalization is required.

[2] Vital signs, pulse ox are required at the following time points (± 5 minutes):

- Screening

During exploration:

[redacted]

During expansion:

[redacted]

Note: Vitals and pulse oximetry should be taken as close to the exact nominal time point as noted above.
Note: [redacted] during infusion timepoint is relative to AMG 994 infusion.
Note: EOI and Post-EOI timepoints for all combination cycles are relative to AMG 404 infusion.

[3] WOCBP, a urine pregnancy test is required at least Q4W thereafter prior to day 1 dosing of all cycles

[4] Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN/total urea, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein

[5] ACTH to be done once every cycle. ANA and ANCA to be done at screening and then if clinically indicated.

[6] Radiological imaging and tumor assessments are required at screening, cycle 1 [redacted] thereafter (C3D[redacted] C5D[redacted] C7D[redacted] and EOT [redacted] Every assessment must include the chest, abdomen, and pelvis and all other known sites of disease. Tumor burden assessments will be performed based on RECIST 1.1 guidelines (Section 11.11). Radiographic response (CR and PR) requires confirmation by a repeat assessment at least 4 weeks after the first detection of response. All subjects must have MRI of the brain performed within 28 days prior to enrollment. Only if MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain scans may be performed at any time if subject has history of CNS disease or as clinically indicated. Any supplemental imaging used to evaluate or determine response by sites should be sent along with the required scans to the central imaging vendor promptly upon completion.

[7] AMG 994 will be administered [redacted]

[8] Subjects will be hospitalized for a minimum of 24 hours following each infusion during the first cycle of treatment on study and following the week 1 infusion of the second cycle of treatment on study. Hospitalization should be extended if any adverse event, clinical change, or safety concern associated with the infusion is observed. This will be based on investigator and Amgen Medical Monitor discretion. Subjects will be observed for 6 hours following each remaining infusion (weeks 2, 3, and 4) during the second cycle of treatment on study and observed for 2 to 4 hours following each subsequent infusion for observation of any side effects.

[9] PK blood samples for AMG 994 and AMG 404 should be collected at the exact nominal time point relative to their respective end of infusions as noted above [see hours (relative to end of infusion) rows for AMG 994 and AMG 404]. If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations. For cycles 3+, AMG 404 PK samples should be collected at predose on day 1 of every cycle and at end of infusion at every other cycle on day 1 starting in cycle 3 (ie, day 1 of cycles 3, 5, 7 and so on).

[10] A tumor biopsy is required at baseline. Tumor tissue (archival within < 6 months of enrollment or recent acquisition) must be available for correlative studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or unstained slides) by study personnel for performance of correlative tissue studies. Fresh tumor biopsies are required for subsequent time points. [redacted]

[11] Safety follow-up visit will occur 30 (+7) days and 140 days (±1 week) after the last dose of AMG 994 and AMG 404 combination therapy.

[12] Long-term follow-up phone call at 6 months (±1 week) after the last dose to collect information on adverse events, serious adverse events, concomitant medications, start of new therapies, and disease status. **After end of study, serious adverse events suspected to be related to investigational products that the investigator becomes aware of, will be reported to Amgen. As a study endpoint is overall survival, the investigator will also need to collect/report fatal serious adverse events (regardless of causality) to Amgen within 24 hours following the investigator's awareness of the event.**

[13] Physical exam is required on days [redacted] of each cycle. Height will be measured at screening only. Weight will be measured at screening and each study

[redacted]

AMG 404 to be administered on [redacted] after the end of infusion of AMG 994 if a ≥ grade 2 infusion reaction is not observed. The dose is [redacted]

Table 1-4. Schedule of Activities: Dose Expansion Cycle 1 - AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	

GENERAL AND SAFETY ASSESSMENTS																										
Informed consent	X																									
Inclusion and exclusion criteria	X																									
Demographics	X																									
Physical examination, ECOG PS[13]	X	X													X											
Medical history	X																									

Footnotes defined on last page of this table

Table 1-4. Schedule of Activities: Dose Expansion Cycle 1 - AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
ECG triplicate measurement[1]	
Vital signs, pulse ox[2]	X
Adverse events review	
Serious adverse events	
Concomitant medication review	

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Table 1-4. Schedule of Activities: Dose Expansion Cycle 1 - AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
LABORATORY ASSESSMENTS	
Pregnancy test (females of childbearing potential only)[3]	X X
Coagulation	X X X X X X X
Hematology	X X X X X X X
Chemistry[4]	X X X X X X X
HIV, Hepatitis B and C screening	X

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Footnotes defined on last page of this table

Table 1-4. Schedule of Activities: Dose Expansion Cycle 1 - AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]																								
WEEKS																									
DAYS																									
Hours (relative to AMG 994 end of infusion)																									
Hours (relative to AMG 404 end of infusion)																									
SP74 Ventana MSLN IHC assay[5]	X																								
Urinalysis	X	X													X										
ACTH[6]	X																								
ANA, ANCA[6]	X																								
RADIOLOGICAL ASSESSMENTS																									
CT/MRI and Tumor Burden Assessment[7]	X																								
Brain MRI[7]	X																								

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Footnotes defined on last page of this table

Table 1-4. Schedule of Activities: Dose Expansion Cycle 1 - AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
DOSING	
AMG 994[8]	
AMG 404[15]	
Hospitalization/Observation[9]	
PHARMACOKINETIC ASSESSMENTS AMG 994[10]	
PHARMACOKINETIC ASSESSMENTS AMG 404[10]	

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Footnotes defined on last page of this table

Table 1-4. Schedule of Activities: Dose Expansion Cycle 1- AMG 994 and AMG 404 Combination Therapy

CYCLES	[redacted]																								
WEEKS																									
DAYS																									
Hours (relative to AMG 994 end of infusion)																									
Hours (relative to AMG 404 end of infusion)																									
ARCHIVAL TUMOR TISSUE[11]	X																								
PRE-TREATMENT TISSUE/FRESH TUMOR BIOPSIES[12]	X																								X
WHOLE BLOOD FOR CYTOMETRY	X	X								X		X			X										
SERUM MARKERS		X								X		X	X	X	X							X		X	
PLASMA FOR ctDNA ANALYSIS	X	X													X										
PBMC		X										X	X	X	X									X	
[redacted]																									

(X) = conditional, refer to applicable footnote

ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; ANA = anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibodies; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Coopera[redacted]Performance Status; EOI = end of infusion; EOT = end of treatment; HIV = human immunodeficiency virus; IHC = immunohistochemistry; [redacted]MRI = magnetic resonance imaging; MSLN = mesothelin; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic(s); PR = partial response; WOCBP = women of child bearing potential.

[1] For Dose Expansion, ECGs are required in triplicate approximately 30 to 60 seconds apart and run consecutively at the following time points (± 5 minutes):
As clinically indicated

[2] Vital signs, pulse ox are required at the following time points (± 5 minutes):
Screening
During expansion:
[redacted]

Note: Vitals and pulse oximetry should be taken as close to the exact nominal time point as noted above.
Note: [redacted]during infusion timepoint is relative to AMG 994 infusion.
Note: EOI and Post-EOI timepoints for all combination cycles are relative to AMG 404 infusion.

[3] WOCBP, an initial serum pregnancy test is required prior day 1 of cycle 1; a urine pregnancy test is required at least Q4W thereafter prior to day 1 dosing.

[4] Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN/total urea, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein

[5] SP74 Ventana MSLN IHC assay to be performed for NSCLC squamous cell carcinoma and adenocarcinoma patients only.

[6] ACTH to be done once every cycle. ANA and ANCA to be done at screening and then if clinically indicated.

[7] Radiological imaging and tumor assessments are required at screening, cycle 1 [redacted]. Every assessment must include the chest, abdomen, and pelvis and all other known sites of disease. Tumor burden assessments will be performed based on RECIST 1.1 guidelines (Section 11.11). Radiographic response (CR and PR) requires confirmation by a repeat assessment at least 4 weeks after the first detection of response. All subjects must have MRI of the brain performed within 28 days prior to enrollment. Only if MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain scans may be performed at any time if subject has history of CNS disease or as clinically indicated. Any supplemental imaging used to evaluate or determine response by sites should be sent along with the required scans to the central imaging vendor promptly upon completion.

[8] AMG 994 will be administered [redacted].

[9] During dose expansion, subjects will be observed for 2 to 4 hours following each infusion for observation of any side effects.

[10] PK blood samples for AMG 994 and AMG 404 should be collected at the exact nominal time point relative to their respective end of infusions as noted above [see hours (relative to end of infusion) rows for AMG 994 and AMG 404]. If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations.

[11] If available, archived tumor tissue (archival within < 6 months of enrollment) or recent acquisition will be collected prior to cycle 1, day 1 during screening.

[12] A tumor biopsy is required at baseline. Tumor tissue (archival within < 6 months of enrollment or recent acquisition) must be available for correlative studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or unstained slides) by study personnel for performance of correlative tissue studies. Fresh tumor biopsies are required for subsequent time points. [redacted]

[13] Physical exam is required on days [redacted] of each cycle. Height will be measured at screening only. Weight will be measured at screening and each study visit where a physical exam is also performed.

[redacted]

[15] AMG 404 to be administered on [redacted] after the end of infusion of AMG 994 if a ≥ grade 2 infusion reaction is not observed. The dose is [redacted]

Table 1-5. Schedule of Activities: Dose Expansion AMG 994 and AMG 404 Combination Therapy Cycle 2 and Beyond

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
GENERAL AND SAFETY ASSESSMENTS	
Physical examination, ECOG PS[13]	X X X X X
ECG triplicate measurement[1]	
Vital signs, pulse ox[2]	◄——► ◄——► ◄——►

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Table 1-5. Schedule of Activities: Dose Expansion AMG 994 and AMG 404 Combination Therapy Cycle 2 and Beyond

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
Adverse events review	◄———
Serious adverse events	◄———
Concomitant medication review	◄———
LABORATORY ASSESSMENTS	
Pregnancy test (females of childbearing potential only)[3]	X X X X X X
Coagulation	X X X X X X X X X X X X

Footnotes defined on last page of this table

Table 1-5. Schedule of Activities: Dose Expansion AMG 994 and AMG 404 Combination Therapy Cycle 2 and Beyond

CYCLES	[redacted]																														
WEEKS																															
DAYS																															
Hours (relative to AMG 994 end of infusion)																															
Hours (relative to AMG 404 end of infusion)																															
Hematology	X					X				X					X					X					X					X	X	
Chemistry[4]	X					X				X					X					X					X					X	X	
HIV, Hepatitis B and C screening																																
Urinalysis	X									X										X										X	X	
ACTH[5]	X									X										X												
ANA, ANCA[5]																																

Footnotes defined on last page of this table

Table 1-5. Schedule of Activities: Dose Expansion AMG 994 and AMG 404 Combination Therapy Cycle 2 and Beyond

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
RADIOLOGICAL ASSESSMENTS	
CT/MRI and Tumor Burden Assessment[6]	X ... X
Brain MRI[6]	X ... X
DOSING	
AMG 994[7]	X ... X ... X
AMG 404[15]	(X) ... (X) ... (X)
Hospitalization/Observation[8]	(X) ... (X) ... (X)

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Footnotes defined on last page of this table

Table 1-5. Schedule of Activities: Dose Expansion AMG 994 and AMG 404 Combination Therapy Cycle 2 and Beyond

CYCLES	[redacted]																																
WEEKS																																	
DAYS																																	
Hours (relative to AMG 994 end of infusion)																																	
Hours (relative to AMG 404 end of infusion)																																	
PHARMACOKINETIC ASSESSMENTS AMG 994[9]	X		X		X				X		X		X							X		X							X	X		
PHARMACOKINETIC ASSESSMENTS AMG 404[9]	(X)					(X)					(X)					(X)				(X)					(X)				X	X		
PRE-TREATMENT TISSUE/FRESH TUMOR BIOPSIES[10]																																	

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Footnotes defined on last page of this table

Table 1-5. Schedule of Activities: Dose Expansion AMG 994 and AMG 404 Combination Therapy Cycle 2 and Beyond

CYCLES	[redacted]
WEEKS	
DAYS	
Hours (relative to AMG 994 end of infusion)	
Hours (relative to AMG 404 end of infusion)	
WHOLE BLOOD FOR CYTOMETRY	X X X X X X
SERUM MARKERS	X X X X X X
PLASMA FOR ctDNA ANALYSIS	X X X X X X
PBMC	X X X X X X
[redacted]	
Phone Call[12]	X

(X) = conditional, refer to applicable footnote

ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; ANA = anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibodies; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOT = end of treatment; HIV = human immunodeficiency virus; [redacted]TFU = long-term follow-up; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic(s); PR = partial response; SFU = safety follow-up; WOCBP = women of child bearing potential.

[1] For Dose Expansion, ECGs are required in triplicate approximately 30 to 60 seconds apart and run consecutively at the following time points:
As clinically indicated
[2] Vital signs, pulse ox are required at the following time points:
Screening
During expansion:
[redacted]

Note: Vitals and pulse oximetry should be taken as close to the exact nominal time point as noted above, ±5 minutes.
Note: [redacted]during infusion timepoint is relative to AMG 994 infusion.
Note: EOI and Post-EOI timepoints for all combination cycles are relative to AMG 404 infusion for combination therapy cycles and relative to AMG 994 for monotherapy cycles.

[3] WOCBP, a urine pregnancy test is required at least Q4W thereafter prior to day 1 dosing of all cycles
[4] Chemistry to include: albumin, alkaline phosphatase, ALT, AST, BUN/total urea, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein
[5] ACTH to be done once every cycle. ANA and ANCA to be done at screening and then if clinically indicated.
[6] Radiological imaging and tumor assessments are required [redacted] (C3[redacted] C5[redacted] C7[redacted] ±7 days) and EOT [redacted] Every assessment must include the chest, abdomen, and pelvis and all other known sites of disease. Tumor burden assessments will be performed based on RECIST 1.1 guidelines (Section 11.11). Radiographic response (CR and PR) requires confirmation by a repeat assessment at least 4 weeks after the first detection of response. All subjects must have MRI of the brain performed within 28 days prior to enrollment. Only if MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain scans may be performed at any time if subject has history of CNS disease or as clinically indicated. Any supplemental imaging used to evaluate or determine response by sites should be sent along with the required scans to the central imaging vendor promptly upon completion.
[7] AMG 994 will be administered [redacted]
[8] During dose expansion, subjects will be observed for 2 to 4 hours following each infusion for observation of any side effects.
[9] PK blood samples for AMG 994 and AMG 404 should be collected at the exact nominal time point relative to their respective end of infusions as noted above [see hours (relative to end of infusion) rows for AMG 994 and AMG 404]. If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations. For AMG 404, PK samples should be collected at (1) predose on day 1 of every cycle and (2) end of infusion on day 1 of cycle 2 and day 1 of every other cycle starting in cycle 3 (ie, day 1 of cycles 3, 5, 7 and so on).
[10] Fresh tumor biopsies are required for subsequent time points. [redacted]
[11] Safety follow-up visit will occur [redacted]days after the last dose of AMG 994 and AMG 404 combination therapy.
[12] Long-term follow-up phone call at 6 months (± 1 week) after the last dose to collect information on adverse events, serious adverse events, concomitant medications, start of new therapies, and disease status. **After end of study, serious adverse events suspected to be related to investigational products that the investigator becomes aware of, will be reported to Amgen. As a study endpoint is overall survival, the investigator will also need to collect/report fatal serious adverse events (regardless of causality) to Amgen within 24 hours following the investigator's awareness of the event.**
[13] Beginning with cycle 3 and subsequent cycles, physical exam is required on days [redacted] of each cycle. Height will be measured at screening only. Weight will be measured at screening and each study visit where a physical exam is also performed.

[redacted]

[15] AMG 404 to be administered on [redacted] after the end of infusion of AMG 994 if a ≥ grade 2 infusion reaction is not observed. The dose is [redacted]

2. Introduction

2.1 Study Rationale

AMG 994 is a bivalent bispecific monoclonal IgG1 directed against MSLN and CD40. This study will evaluate AMG 994 monotherapy and in combination with AMG 404, an anti-PD-1 checkpoint monoclonal antibody (mAb), for the treatment of patients with locally-advanced or metastatic advanced solid tumors reported to express MSLN.

Mesothelin is a cell-surface glycoprotein with normal expression limited to mesothelial cells lining the surface of several body cavities, including the pleura, peritoneum, and pericardium, and covering the surface of multiple internal organs. Expression of MSLN is upregulated in many solid tumors during the tumorigenic process, with particularly high expression in NSCLC, mesothelioma, pancreatic cancer, and serous ovarian cancer. Higher expression of MSLN has been correlated with poorer patient prognosis across multiple tumor types, including ovarian cancer, bile duct cancer, lung adenocarcinoma, triple-negative breast cancer, and resectable pancreatic cancer (Hassan et al, 2016). Based on these findings, MSLN is an attractive target for cancer therapy with antibody-based approaches as well as tumor vaccines (Awuah et al, 2016).

CD40 is a member of the tumor necrosis factor (TNF) receptor superfamily that is preferentially expressed by antigen presenting immune cells, such as dendritic cells, B cells, and macrophages. Interaction with its trimeric ligand, CD40L, expressed by activated T helper cells leads to CD40-mediated activation of antigen presenting cells, potentiating expression of antigen presentation machinery, T cell co-stimulatory molecules, and pro-inflammatory cytokines. CD40 function is critical for the generation of robust and long-lasting cell-mediated immunity (Schaer et al, 2014; Bennett et al, 1998; Ridge et al, 1998) and activation of CD40 has been widely explored as an immunotherapeutic approach for the treatment of cancer (Schaer et al, 2014; Vonderheide and Glennie, 2013).

Systemic non-tumor targeted CD40 agonist monoclonal antibodies have been associated with dose-limiting, immune-mediated adverse events such as cytokine release syndrome (CRS), thrombocytopenia, and elevated liver function tests (Irenaeus et al, 2019; Vitale et al, 2019; Johnson et al, 2015; Vonderheide et al, 2007; Vonderheide et al, 2001). To limit systemic CD40 activation and associated key safety risks and induce robust CD40 activation of antigen presenting immune cells locally in solid tumors, Amgen has developed AMG 994, a bispecific monoclonal immunoglobulin targeting MSLN and CD40 that has been shown to be a potent, MSLN-dependent CD40

agonist in nonclinical studies. Given the route of administration, an infusion-related reaction is still considered a key safety risk for AMG 994. Another bispecific molecule targeting CD40 and MSLN, ABBV-428, has been shown to enhance tumor-specific immunity in nonclinical studies (Ye et al, 2019) and is being evaluated in a clinical program including a recently completed phase 1 dose escalation clinical study (Fang et al, 2020; Luke et al, 2019; National Library of Medicine, NCT02955251, 2019).

Generation of productive anti-tumor immunity is a multi-step process consisting of tumor-specific T cell activation, differentiation, and expansion in tumor-draining lymph nodes, trafficking of tumor-specific T cells into tumor tissue, and direct interactions between tumor cells and T cells leading to T cell activation and tumor cell death (Chen and Mellman, 2013). The PD-1 receptor functions as a dominant inhibitor of anti-tumor T cell responses. Its expression is rapidly upregulated by T cells after activation and sustained at high levels by populations of tumor-specific T cells within the tumor microenvironment (Ribas and Wolchok, 2018). Interactions between PD-1 expressed by T cells and its ligands PD-L1 and programmed death ligand 2 (PD-L2) expressed by tumor cells and antigen presenting cells of the immune system can inhibit generation of tumor-specific T cells in the lymph node and cytolytic killing activity of T cells in the tumor.

Enhancement of anti-tumor immunity through inhibition of PD-1 has been effective in the treatment of many malignancies. AMG 404 is a fully human mAb that binds human and cynomolgus monkey PD-1 and blocks the ability of these receptors to interact with human ligands, PD-L1, and PD-L2. Anti-PD-1 and anti-PD-L1 therapies have demonstrated improved overall survival and/or objective responses in multiple advanced solid tumors; however, optimal therapy will likely require combining anti-PD-1 mAb treatment with other therapies. AMG 404 is currently being evaluated in subjects with advanced solid tumors in Study 151001. Clinical results to date indicate that AMG 404 is well tolerated at doses up to [redacted] with 3 key safety risks: infusion-related reaction, immune-related toxicities, and embryofetal toxicity.

A recent review by Vonderheide (2020) of clinical experience with CD40 agonist antibodies suggests limited monotherapy efficacy, but the potential to show increased efficacy with other immunotherapies, such as PD-1 blockade. Amgen proposes that the novel-novel combination of AMG 994, a CD40 agonist designed to limit systemic toxicities by MSLN-dependent-activation, and AMG 404, a molecule that can block

PD-1-mediated T cell inhibition, may promote greater responses in multiple advanced solid tumor types than either therapy alone.

Amgen plans to conduct a FIH phase 1 Study 20190136 in adult subjects with locally-advanced or metastatic advanced solid tumors reported to express MSLN, which includes evaluation of AMG 994 in combination with AMG 404 administered until evidence of disease progression; intolerance to study medication; withdrawal of consent; or, in the absence of the above, up to 12 months if subject achieves a complete response, and up to 24 months if partial response or stable disease. Study assessments will include measures of safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary anti-tumor activity.

2.2 Background

2.2.1 Disease

Mesothelin is a cell-surface glycoprotein with normal expression limited to mesothelial cells lining the surface of several body cavities, including the pleura, peritoneum, and pericardium, and covering the surface of multiple internal organs. Expression of MSLN is upregulated in many solid tumors during the tumorigenic process, with particularly robust expression in mesothelioma, serous ovarian cancer, NSCLC, and pancreatic cancer. Higher expression of MSLN has been correlated with poorer patient prognosis across multiple tumor types, including ovarian cancer, bile duct cancer, lung adenocarcinoma, triple-negative breast cancer, and resectable pancreatic cancer (Hassan et al, 2016). Five-year survival rates are as follows: pancreatic adenocarcinoma 3%, mesothelioma less than 10%, lung adenocarcinoma less than 30%, high grade ovarian cancer 25 %. Based on these findings, MSLN is an attractive target for cancer therapy with antibody-based approaches as well as tumor vaccines (Awuah et al, 2016).

Interaction with its trimeric ligand, CD40L, expressed by activated T helper cells leads to CD40-mediated activation of antigen presenting cells potentiating expression of antigen presentation machinery, T cell co-stimulatory molecules, and pro-inflammatory cytokines. CD40 function is critical for the generation of robust and long-lasting cell-mediated immunity critical for the generation of robust and long-lasting cell-mediated immunity (Schaer et al, 2014; Bennett et al, 1998; Ridge et al, 1998) and activation of CD40 has been widely explored as an immunotherapeutic approach for the treatment of cancer (Schaer et al, 2014; Vonderheide and Glennie, 2013).

AMG 994 (MSLN-dependent CD40 agonist) and AMG 404 (PD-1 inhibitor) target distinct steps in the anti-tumor immune response. By activating the CD40 receptor on antigen presenting cells, AMG 994 promotes initiation of anti-tumor T-cell responses while AMG 404 further enhances these T-cell responses by blocking PD-1-mediated inhibitory signals.

The combination of AMG 994 and AMG 404 is not predicted to result in synergistic increases or significant overlapping toxicity based on differing modes of action (Vonderheide, 2018; Piechutta and Berghoff, 2019), and differing safety profiles in nonclinical monotherapy toxicology studies (Study 151001; AMG 404: Section 2.6.6, IND 140964). By targeting orthogonal processes in the anti-tumor T cell response, AMG 994 and AMG 404 may synergize to promote efficacy.

Clinical experience with CD40 agonist antibodies suggests limited monotherapy efficacy, as reviewed in Vonderheide (2020), but the potential to combine well with other immunotherapies, such as PD-1 blockade. Activation of CD40 on antigen presenting cells leads to upregulation of antigen presenting cell machinery, T cell co-stimulatory molecules, and pro-inflammatory cytokines, all of which can serve to promote and sustain anti-tumor T cell responses. Thus, by targeting orthogonal processes in the anti-tumor immune response, therapeutics designed to inhibit the function of PD-1 (AMG 404) and promote the activity of CD40 (AMG 994) may synergize to potentiate generation of tumor-specific cytolytic T cells and promote therapeutic efficacy.

Consistent with this hypothesis, in vivo studies in the huEPCAM-MC38 syngeneic mouse tumor model using the AMG 994 mouse surrogate (muCD40 BsAb) and an antibody that inhibits interaction between murine PD-1 and PD-L1 (anti-PD-L1; AMG 404 mouse surrogate) have demonstrated the ability of this combination to promote increased complete tumor regression relative to either individual treatment alone or the combination of a nontargeted systemic CD40 agonist (anti-CD40) with anti-PD-L1.

Thus, the combination of AMG 994, a molecule that may promote CD40-mediated initiation of anti-tumor T cell responses with limited systemic toxicities, and AMG 404, a molecule that can block PD-1-mediated T cell inhibition downstream of these initiation events, may promote greater responses in multiple advanced solid tumor types than either therapy alone.

2.2.2 Amgen Investigational Product Background: AMG 994

AMG 994 is a fully human bivalent bispecific monoclonal IgG1 SEFL2 directed against MSLN and CD40, expressed in a Chinese hamster ovary cell line with a molecular weight of approximately 196 kDa. [redacted]

A detailed description of the chemistry, pharmacology, efficacy, and safety of AMG 994 is provided in the AMG 994 Investigator's Brochure.

2.2.2.1 AMG 994 Toxicology

The nonclinical safety assessment was performed in accordance with ICH Guideline S9, "Nonclinical Evaluation for Anticancer Pharmaceuticals" (ICH, 2010) and consisted of an exploratory 17-day repeat dose study in the cynomolgus monkey, a Good Laboratory Practice (GLP)-compliant [redacted] repeat dose study in the cynomolgus monkey, an in vitro human cytokine release assay, and an in vitro platelet activation assay. The cynomolgus monkey was selected as the pharmacologically relevant species for nonclinical safety assessment based on similar binding and functional activity of the CD40 and MSLN arms of AMG 994 for human and cynomolgus monkey, but not mouse or rat.

In the [redacted] GLP study AMG 994 was administered intravenously to cynomolgus monkeys weekly for 4-weeks at doses of [redacted] mg/kg. The doses were selected to appropriately characterize toxicity, toxicokinetic parameters, and establish a highest non-severely toxic dose (HNSTD) while ensuring maximum CD40 receptor occupancy (RO). The [redacted] route of administration was chosen based on the intended clinical route of administration. AMG 994-related changes in this study were limited to [redacted]

[redacted] The HNSTD was [redacted], the highest dose tested.

The potential for AMG 994-mediated cytokine release was in a human cytokine release assay. AMG 994 did not induce increases of measured cytokines above background levels in the absence of MSLN expressing cells as predicted based on the requirement for MSLN binding and CD40 crosslinking for AMG 994 mediated agonism. Consistent with these in vitro results, AMG 994 did not cause cytokine release at any dose level in the cynomolgus monkey during the GLP toxicology study.

Additionally, the potential for AMG 994-mediated platelet activation was assessed in a human platelet activation assay. AMG 994 did not induce platelet activation in human whole blood at any of the concentrations tested in the absence of MSLN expressing cells as predicted based on requirement for MSLN binding and CD40 crosslinking for AMG 994 mediated agonism. A lack of AMG 994-associated platelet activation is further supported by no platelet count changes in the cynomolgus monkey during the GLP toxicology study.

2.2.3 Amgen Investigational Product Background: AMG 404

AMG 404 is a fully human, monoclonal IgG1 SEFL2 directed against PD-1, expressed in a Chinese hamster ovary cell line. [redacted]

A detailed description of the chemistry, pharmacology, efficacy, and safety of AMG 404 is provided in the AMG 404 Investigator's Brochure.

2.3 Benefit/Risk Assessment

This is a FIH study with AMG 994 monotherapy and AMG 994 in combination with AMG 404. Data from nonclinical toxicity studies of AMG 994 and clinical and nonclinical studies with AMG 404 suggest that the potential benefit/risk profile favors clinical development of AMG 994 in combination with AMG 404 for patients with advanced solid

tumors of types known to express MSLN. 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.

2.3.1 AMG 994

2.3.1.1 Therapeutic Context

AMG 994 will be investigated with advanced solid tumors of types known to express MSLN. Mesothelin is expressed by many solid tumors, with particularly high expression in NSCLC adenocarcinoma, mesothelioma, pancreatic adenocarcinoma, and high-grade serous ovarian cancer. Higher expression of MSLN has been correlated with poorer prognosis for patients with ovarian cancer, cholangiocarcinoma, lung adenocarcinoma, triple negative breast cancer, and resectable adenocarcinoma. The 5-year survival rates are as follows:

- Lung adenocarcinoma, less than 30%
- Mesothelioma, less than 10%
- Pancreatic adenocarcinoma, 3%
- High grade ovarian cancer, 25%

2.3.1.2 Key Benefits

As AMG 994 is in early development and there is no human or clinical experience with AMG 994, key benefits are being investigated and will be described when the data become available.

2.3.1.3 Key Risks

AMG 994 has not been administered to humans, there is no human or clinical experience with AMG 994. Based on biological mechanism of action, nonclinical toxicity studies of AMG 994, and clinical experience with other CD40 agonists, the key safety risks for AMG 994 include infusion-related reactions (see Table 2-1).

Systemic CD40 molecules have been associated with higher frequency of adverse events such as CRS, thrombocytopenia and elevations in liver enzymes, however since there is requirement for MSLN binding and CD40 crosslinking for AMG 994 mediated agonism it is unlikely these adverse events will be observed with AMG 994. Overall, the results of the nonclinical safety studies support the initiation of AMG 994 clinical studies.

Table 2-1. Key Safety Risks for AMG 994

Safety Risk	Description
Infusion-related reactions	Signs and symptoms may include pyrexia, chills, rigors, flushing, urticaria, hypotension, dyspnea, wheezing, headache, back pain, and abdominal pain.

Clinical signs and symptoms of infusion-related reactions, along with safety laboratory parameters, will be monitored during the study to ensure subjects' safety. Refer to Section 11.10 for specific recommendations regarding the mitigation and management of infusion-related reactions.

Refer to the AMG 994 Investigator's Brochure for further description of key safety risks

2.3.2 AMG 404

2.3.2.1 Therapeutic Context

AMG 404 is currently being investigated in subjects with advanced solid tumors as a monotherapy and in combination with other investigational agents and, in this study, will be investigated in combination with AMG 994 in subjects with advanced solid tumors of types known to express MSLN.

2.3.2.2 Key Benefits

The PD-1 receptor-ligand interaction is a major pathway that tumors use to suppress immune control. Programmed cell death-1 has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) and limit the efficacy of immune therapies. Enhancement of anti-tumor immunity through inhibition of PD-1 has been effective in treatment of many malignancies. AMG 404 is a mAb that binds to PD-1 and may provide clinical benefit in combination with AMG 994.

2.3.2.3 Key Risks

AMG 404 is currently being tested as monotherapy for the first time in humans with advanced solid tumors in the Amgen-sponsored Study 20180143. As of 04 May 2020, 62 subjects have received AMG 404 at doses between [redacted] and has been well-tolerated. Key safety risks for AMG 404 include immune-related toxicities, infusion-related reactions, and embryo-fetal toxicity (see Table 2-2). Among immune related toxicities, more recently hypothyroidism has been identified as an adverse drug reaction (ADR).

Table 2-2. Key Safety Risks for AMG 404

Safety Risk	Description
Immune-related toxicities	Immune-related adverse effects associated with PD-1 blocking agents include pneumonitis, colitis, hepatitis, endocrinopathies including hypothyroidism, nephritis and renal dysfunction, skin reactions, encephalitis, and other immune-related adverse reactions.
Infusion-related reactions	Signs and symptoms may include pyrexia, chills, rigors, flushing, urticaria, hypotension, dyspnea, wheezing, headache, back pain, and abdominal pain.
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 administered during pregnancy (Poulet et al, 2016).

Clinical signs and symptoms of immune-related toxicities and infusion-related reactions, along with safety laboratory parameters, will be monitored during the study to ensure subjects' safety. Refer to Section 11.10 for specific recommendations regarding the mitigation and management of immune-related toxicities and infusion-related reactions.

Refer to the AMG 404 Investigator's Brochure for further description of key safety risks.

2.3.3 AMG 994 in Combination with AMG 404

AMG 994 will be used in combination with AMG 404. Based on biological mechanism of action and initial clinical safety information from the ongoing FIH study with AMG 404 (Study 20180143), the key safety risks described for AMG 404 monotherapy including immune related toxicities (with hypothyroidism now as an ADR) and embryofetal toxicity would also be expected.

With the exception of infusion-related reactions, which is a key safety risk for both AMG 994 and AMG 404, the combination of AMG 994 and AMG 404 is not anticipated to have synergistic increases or additional overlapping toxicity based on differing mechanisms of action (Piechutta and Berghoff, 2019; Vonderheide, 2018) and differing adverse events reported in nonclinical monotherapy toxicology studies (AMG 994: ongoing; AMG 404: Section 5 of Investigator's Brochure, Appendix 2).

Safety of combination therapy will be monitored by routine safety parameters (adverse events, laboratory data, etc.) collected during the study. The risk of synergistic toxicity is anticipated to be low due to different modes of clearance and modes of action. Refer to the protocol schedule of assessments for specific information regarding the safety monitoring parameters.

Finally, sucrose-mediated renal toxicity is an additional risk which may increase during combination therapy and will be monitored during the study.

The drug product for AMG 994 and AMG 404 contains 9% sucrose as a stabilizer. In accordance with the dosing schedule, using the anticipated maximum doses of AMG 994 ([redacted]) in combination with AMG 404 ([redacted]), the estimated toxicology-based limit for parenteral administration of sucrose or per dose limit of > 3.5 g of sucrose is not expected to be exceeded.

Monitoring of renal function (eg, serum creatinine, electrolytes) and any potential renal dysfunction associated adverse events will be conducted during the study. Subject eligibility criteria, monitoring, and dose modification guidelines pertaining to renal function are provided in the clinical study protocol.

The above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the respective Investigator's Brochure for further data on AMG 994 and AMG 404.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety, tolerability, and maximum tolerated dose (MTD)/maximum tolerated combination dose (MTCD) or recommended phase 2 dose (RP2D) of AMG 994 as monotherapy and AMG 994 in combination with AMG 404 in subjects with advanced solid tumors	• Dose-limiting toxicities (DLTs) • Treatment-emergent and treatment related adverse events (including all adverse events, grade ≥ 3, serious adverse events, fatal adverse events, adverse events requiring permanent discontinuation of study treatment, and immune-related events) • Changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
Secondary	
• Preliminary evaluation of anti-tumor activity of AMG 994 as monotherapy and AMG 994 in combination with AMG 404	• Objective response (OR) per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • Duration of response (per modified RECIST 1.1)

	• Overall survival (OS) • Progression-free survival (per modified RECIST 1.1) • Time to progression (per modified RECIST 1.1) • Time to subsequent therapy
• Characterize the PK of AMG 994 monotherapy and AMG 994 in combination with AMG 404	PK parameters • Maximum serum concentration (C_{max}) • Minimum serum concentration (C_{min}) • Area under the concentration-time curve (AUC) over the dosing interval • Half-life ($t_{1/2}$), if feasible

Exploratory
[redacted]

4. Study Design

4.1 Overall Design

This is a FIH, multicenter, non-randomized, open-label, phase 1 study to evaluate the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary efficacy of multiple doses of AMG 994 monotherapy and multiple doses of AMG 994 in combination with AMG 404 in subjects with locally-advanced or metastatic solid tumors reported in the literature to express MSLN including mesothelioma, NSCLC squamous cell carcinoma (Part 2 only) and adenocarcinoma (Part 1 and Part 2), pancreatic adenocarcinoma, and high grade serous ovarian carcinoma (platinum resistant). Table 4-1 summarizes tumor histologies known to express MSLN (Hassan et al 2016), and will be used as a reference for eligibility to enroll to Dose Escalation (Part 1). Except for NSCLC subjects enrolled to Dose Expansion (Part 2), subjects will not be

required to undergo testing to confirm tumor MSLN expression to be enrolled into the study.

Table 4-1: MSLN Expression in Solid Tumors

Tumor Type	Patients with MSLN Expression – Positive Disease (%)
Mesothelioma	82
Epithelioid	95
Sarcomatoid	0
Pancreatic adenocarcinoma	85
Epithelial ovarian cancer	70
High-grade serous	75
Endometrioid	69
Mucinous	11
Clear cell	52
NSCLC	57
Adenocarcinoma	64
Squamous	21
SCLC	0
Esophageal cancer	28
Gastric cancer	47
Biliary cancer	
Extrahepatic	95
Intrahepatic	10
Other or unspecified	42
Colorectal cancer	30
Cervical cancer	25
Endometrial cancer	59
Breast cancer	
Triple negative	66
Other	1.6
Unspecified	9

MSLN = mesothelin, NSCLC = nonsmall-cell lung cancer

Study assessments will include measures of safety, tolerability, PK, and pharmacodynamics, immunogenicity, and preliminary anti-tumor activity.

AMG 994 will be administered by [redacted] cycle (on days [redacted]) and AMG 404 will be administered by [redacted] cycle. The study will be conducted in 2 parts: Part 1 – Dose Exploration and Part 2 – Dose Expansion. Part 1 is aimed at evaluating the safety, tolerability, PK, and pharmacodynamics of AMG 994 and AMG 404 combination using sequential and concurrent initiation of dosing: (a) 1 cycle of AMG 994 monotherapy followed by combination of AMG 994 and AMG 404 from cycle 2 onwards and (b) AMG 994 and AMG 404 dosing starting on cycle 1 day 1. The MTD/MTCD of the combination in subjects with locally advanced or metastatic solid tumors will be determined using a Bayesian Logistics Regression Model (BLRM) design. Part 2 will further evaluate the safety of the MTD/MTCD and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) of the combination in specific tumor types.

The dose expansion part of the study (Part 2) will be opened once the MTD/MTCD/RP2D of the combination has been determined in Part 1.

During Dose Exploration (Part 1), 94 subjects will be enrolled with metastatic or locally advanced solid tumors of types known to express MSLN for which no standard systemic therapy exists; screening for MSLN expression will not occur. During Dose Expansion (Part 2), approximately 120 additional subjects, up to 30 subjects in each of 4 tumor types (mesothelioma, NSCLC squamous cell carcinoma and adenocarcinoma [if upon screening found to be MSLN positive], pancreatic adenocarcinoma, and high grade serous ovarian carcinoma) will be enrolled; screening for MSLN expression will be required for subjects with NSCLC. The DLT evaluation period will be [redacted] for each cycle. Administration of AMG 994 (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 subject achieves a complete response, and up to 24 months if partial response or stable disease.

Part 1 - Dose Exploration

Dose exploration cohorts will estimate the safety, tolerability, PK, and pharmacodynamics of different doses of AMG 994 in combination with AMG 404 in subjects with advanced solid tumors of types known to express MSLN. The dose exploration will be conducted in 2 parts (Section 1.2):

Part 1a will include [redacted] of 3 to 6 subjects each.

[redacted]

Part 1b:

Part 1c:

The decision to advance to the next dose level will be recommended by the DLRT using the dose level recommendation from BLRM model, as appropriate, and by evaluating available safety data, laboratory, and PK information. For each DLT or suspected DLT, the BLRM model will be updated and reviewed by Amgen safety and the medical monitor and, as appropriate, an ad hoc DLRM may be called.

To ensure the safety of all subjects, risk mitigation plans will be followed (see Section 6.2.1).

Dose exploration will continue until any of the following events:

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

Part 2 – Dose Expansion

Upon completing the dose exploration phase of the study, and depending on data obtained, dose expansion may proceed in subjects with certain advanced solid tumors of types known to express MSLN:

- Mesothelioma
- NSCLC squamous cell carcinoma and adenocarcinoma, if upon screening found to be MSLN positive
- Pancreatic adenocarcinoma
- High grade ovarian carcinoma (platinum resistant)

AMG 994 plus AMG 404 combination will be administered from cycle 1, day 1.

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 214 subjects with advanced solid tumors of types known to express MSLN will be enrolled in the study. Up to 94 evaluable subjects will be enrolled in dose escalation (Part 1) and approximately 120 evaluable subjects will be enrolled in dose expansion (Part 2), up to 30 subjects in each of 4 tumor types (mesothelioma, NSCLC squamous cell carcinoma and adenocarcinoma [if upon screening are found to be MSLN positive], pancreatic adenocarcinoma, and high grade serous ovarian carcinoma).

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

Ineligible subjects (ie, subjects who were exposed to investigational product but post hoc were found to be ineligible) may be replaced. During Part 1, subjects who are not DLT-evaluable may be replaced (see Section 6.2.1 for a definition of DLT-evaluable). All available safety data for subjects who are not DLT evaluable will still be evaluated and considered in DLRT recommendations. Refer to Section 7.2.2 for information regarding replacement of subjects who receive AMG 994 in combination with AMG 404. Subjects who are withdrawn or removed from treatment or the study during Part 2 will not be replaced.

4.2.2 Number of Sites

Approximately 30 investigative sites in Australia, Canada, China, Japan, the United States, and some countries of the European Union (EU) will be included in the study. Sites that do not enroll subjects within 6 months of site initiation may be closed.

4.3 Justification for Investigational Product Dose

The proposed starting dose of AMG 994 in the FIH study is [redacted] per dose. This was based on the predicted human dose necessary to provide a maximum serum concentration (C_{max}) approximating the minimum anticipated biological effect level (MABEL). The RO on CD40 was identified as the key in vitro parameter of AMG 994 activity used to estimate the MABEL because the binding of CD40 to the anti-CD40 domain in AMG 994 (dissociation constant [K_d] for binding, K_d [redacted]) is the primary event that triggers the pharmacological activity of AMG 994. It is worth noting that a similar K_d was measured for MSLN RO of AMG 994 in humans. Based on 80% CD40 RO of AMG 994, the MABEL was estimated to be [redacted]

Use of 80% RO as the MABEL and basis for the FIH starting dose is supported by the toxicological and pharmacological data of AMG 994 and external clinical data from a MSLN-dependent CD40 agonist with a similar mechanism of action as AMG 994 demonstrating that AMG 994 is a low risk immune activating agent.

Specifically, data from a 1-month GLP-compliant study in cynomolgus monkeys showed that AMG 994 is well tolerated at doses up to [redacted] with no concerning safety findings. At a starting dose of [redacted] the predicted human exposure based on the area under the curve (AUC) and C_{max} is [redacted]-fold and [redacted]-fold lower than the observed AUC and C_{max} exposure in cynomolgus monkeys at the HNSTD of [redacted]. The lack of concerning safety findings observed in cynomolgus monkeys at approximately [redacted] fold higher exposures than the proposed starting dose in humans is clinically relevant due to cross reactivity of AMG 994 in cynomolgus monkeys further supporting the lack of safety concerns at the proposed starting dose.

AMG 404 will be administered at a fixed dose of [redacted] (RP2D) as part of the AMG 994 plus AMG 404 combination. This dose is supported with data from 59 subjects with advanced or metastatic solid tumors that have been exposed to AMG 404 monotherapy in the ongoing Study 20180143. As a monotherapy, AMG 404 was well tolerated across the [redacted] dose range with no dose-related increases in frequency or severity of adverse events in the population

studied and preliminary RO results confirm PD-1 target coverage in peripheral blood T-cell subsets and are consistent with AMG 404 achieving saturating PD-1 occupancy on total CD3+ T cells, CD4+ T cells, and CD8+ T cells by 4 hours postinfusion with maintenance of saturation.

The combination of AMG 994 plus AMG 404 is not anticipated to have increases or significant overlapping toxicity based on differing mechanisms of action (Piechutta and Berghoff, 2019; Vonderheide, 2018).

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).

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

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (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 [redacted], 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 994 and AMG 404, evidence of clinical and radiologic progression, and willingness to participate in the study.

4.5 Patient Input on Study

Patient input on the design of the study was not obtained.

5. Study Population

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

Eligibility criteria will be evaluated during screening.

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

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

Minor variations to these inclusion and exclusion criteria may be allowed on the basis of agreement reached by the Investigator and Amgen Study Physician, such that recruitment does not compromise either the safety of the study subject involved or the integrity of the study data. Such agreements are to be documented in accordance with Amgen SOPs. The Institutional Review Board/Independent Ethics Committee (IRB/IEC) is required to be notified that an allowance to the criteria had been made.

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/assent prior to initiation of any study specific activities/procedures.

102 Age ≥ 18 years at the time of signing informed consent.

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

104 Dose Exploration (Part 1) and Dose Expansion (Part 2): Subject must have histologically or cytologically proven metastatic or locally advanced solid tumors of known MSLN expression (Table 4-1) who have relapsed after and/or are refractory to established and available therapies with known clinical benefit, for which:

- No standard systemic therapy exists; or
- Standard systemic therapy has failed or is not available.

Note: testing to confirm MSLN expression is not required for study inclusion within Dose Exploration (Part 1). During Dose Expansion (Part 2), subjects with NSCLC will be screened and enrolled if MSLN positive.

105 Dose Expansion (Part 2): Subject must have 1 of the following malignancies: mesothelioma, pancreatic adenocarcinoma, MSLN positive NSCLC squamous cell carcinoma or adenocarcinoma, high grade serous ovarian carcinoma.

106 At least 1 measurable or evaluable lesion as defined by modified RECIST 1.1 guidelines.

107 Subjects must be willing to undergo a biopsy prior to enrollment and during treatment with AMG 994.

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 central nervous system (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 non-serious CNS diseases that are asymptomatic and deemed irreversible (eg, peripheral neuropathy), 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 and has not had a seizure within 1 month prior to the screening visit.

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:

- Estimated glomerular filtration rate based on Modification of Diet in Renal Disease (MDRD) calculation ≥ 45 mL/min/1.73 m^2

112 Hepatic function, as follows:

- Total bilirubin (TBL) ≤ 1.5 x upper limit of normal (ULN) or ≤ 3 x ULN for subjects with liver metastasis

- Aspartate transaminase (AST) ≤ 3 x ULN or ≤ 5 x ULN for subjects with liver metastasis
- Alanine aminotransferase (ALT) ≤ 3 x ULN or ≤ 5 x ULN for subjects with liver metastasis
- Alkaline phosphatase ≤ 2.5 x ULN or ≤ 5 x ULN for subjects with liver metastasis

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 exception[s]:

- Malignancy treated with curative intent and with no known active disease present for ≥ 3 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.

227 Subjects with NSCLC squamous cell carcinoma (Part 1), MSLN negative NSCLC squamous cell carcinoma (Part 2), or MSLN negative NSCLC adenocarcinoma (Part 2) once the subject has been screened for MSLN expression.

228 Subjects with sarcomatoid mesothelioma and small cell lung cancer will be excluded from both the Dose Exploration (Part 1) and Dose Expansion (Part 2) parts of the study.

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, or investigational agent) within 21 days prior to study day 1. Note: Palliative radiotherapy is permitted.

206 Treatment with a checkpoint inhibitor within 9 weeks prior to study day 1.

207 Live vaccine therapy within 4 weeks prior to study drug administration.

208 Current treatment or within 14 days of day 1 with immunosuppressive corticosteroid defined as > 10 mg prednisone daily or equivalent. Steroids with no minimal systemic effect (such as topical or inhalation) are permitted.

Prior/Concurrent Clinical Study Experience

209 Currently receiving treatment in another investigational device or drug study, or less than 21 days prior to study day 1 since ending treatment on another investigational device or drug study(ies).

Diagnostic Assessments

210 Evidence of active or radiological sequelae of non-infectious pneumonitis.

211 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.

212 History of allergic reactions or acute hypersensitivity reaction to antibody therapies.

213 Positive/non-negative test results for human immunodeficiency virus (HIV)

214 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.

215 Active infection requiring oral or intravenous therapy.

216 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.

217 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.

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

- 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 v5.0 grade 1.

- Exception: - clinically stable hypothyroid status managed with hormone replacement therapy, is permitted

Other Exclusions

219 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 6 months after the last dose of AMG 994 and/or AMG 404.

220 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 6 months after the last dose of AMG 994 and/or AMG 404. Refer to Section 11.5 for additional contraceptive information.

221 Female subjects of childbearing potential with a positive pregnancy test assessed at day 1 by a serum pregnancy test.

222 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 8 months after the last dose of AMG 994 and/or AMG 404. Refer to Section 11.5 for additional contraceptive information.

223 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 8 months after the last dose of AMG 994 and/or AMG 404.

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

225 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.

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

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment 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. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

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

5.4 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. 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 Modular Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 6-1 below.

6.1 Treatment(s) Administered

6.1.1 Investigational Products

Table 6-1. Study Treatments

	Amgen Investigational Product:[a]	**Amgen Investigational Product:**[a]
Study Treatment Name	AMG 994	AMG 404
Dosage Formulation	[redacted]	
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Doses will vary across treatment cohorts and will [redacted] Planned AMG 994 dose levels for the dose exploration cohorts are as follows: [redacted] Based on emerging data and DLRM recommendation, intermediate and/or alternative dose levels and schedules (eg, dose dense) may be implemented.	
Route of Administration	[redacted]	
Accountability	The start date, start time, stop date, stop time, dose administered, reason for dose change, and package lot number are to be recorded on each subject's CRF(s).	The start date, start time, stop date, stop time, dose administered, reason for dose change, and package lot number are to be recorded on each subject's CRF(s).
Dosing Instructions	AMG 994 will be administered as an [redacted] at a constant flow rate over [redacted]	AMG 404 will be administered as an [redacted] at a constant flow rate over [redacted] AMG 994 infusion if a ≥ grade 2 infusion reaction is not observed.
Device	Infusion Pump	Infusion Pump

CRF = case report form; DLRM = dose level review meeting; [redacted]

[a] AMG 994 and AMG 404 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Non-investigational Products

This study will not use non-investigational products.

6.1.3 Medical Devices

There are no investigational medical devices in this study.

Amgen investigational products must be administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment. Investigational product solutions for infusion will be prepared in bags for [redacted] and delivered through infusion lines that are both compatible with the investigational products. Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

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

6.1.4 Other Protocol-required Therapies

There are no other protocol-required therapies in this study

6.1.5 Other Treatment Procedures

There are no other protocol-required 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)**, combination product,** or device(s) after it is released for distribution to market or clinic by either **(1)** Amgen or **(2)** distributors **or** partners for whom Amgen manufactures the material. **This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labelling, and inserts.**

This includes any investigational product(s) provisioned and/or repackaged/modified by Amgen**:**

- **AMG 994**
- **AMG 404**

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

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 is not encouraged during the DLT-evaluation period. Once the DLT evaluation period is complete, the use of growth factors can be allowed after discussion with the Amgen medical monitor.

Administration of systemic corticosteroids, immunomodulators, and hormonal replacement therapy for the management of toxicities (eg, immune-related adverse events) is allowed; however, AMG 994 and AMG 404 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 [redacted]
- Major surgery within [redacted]
- Enrollment into another investigational drug or device study

6.2 Dose Modification

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

Sentinel Dosing

During the dose-exploration part of the study, there will be at least a 1-week interval between start of treatment of the first and second subject, in each cohort (ie, at the same

dose for AMG 994 monotherapy and AMG 994 in combination with AMG 404). Prior to start of a new subject, the site investigator of the previous subject will evaluate all available safety and laboratory data for the treated subject and will send written confirmation on occurrence/non-occurrence of a DLT to the sponsor. The sponsor will only be able to approve treatment start for the next subject in the cohort after receipt of this confirmation. If deemed necessary, the 1-week interval may be extended until sufficient data are available to allow an assessment of the feasibility of treatment start of the next subject. In addition to the 1-week interval between treatment start of the first and second subject in each cohort, there will be a 72-hour interval between treatment start of the second and third subject, then all subsequent subjects in each cohort may start treatment. Sentinel dosing may apply during cohort extension, at the Sponsor's discretion, based on available safety data. The same process as described above will apply for determining if subsequent subjects may start treatment.

DLT-evaluable Periods (DLT Windows)

Part 1a will include [redacted] of 3 to 6 subjects each.

[redacted]

Part 1b:

Part 1c:

Dose Level Determination

A recommendation to escalate to a higher dose cohort will only occur when the previous dose regimen has been found to be reasonably tolerated based on available study data through study [redacted] 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).

After all DLT-evaluable subjects have completed the monotherapy DLT window, the first DLRM will be held to review data, monitor safety, and recommend dose changes, if applicable. [redacted].

The review team will be composed of the investigators, Amgen Medical Monitor, Amgen Global Safety Officer (GSO) or designated safety scientist, Amgen Early Clinical Development Manager, and Biostatistics representative. Additional members may be added as needed (eg, Clinical Pharmacologist). 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 investigators.

A quorum, defined as the majority (defined as greater than or equal to 50%) of actively screening and enrolling investigators or their qualified designee (ie, sub-investigator), must be in attendance for DLRM to proceed. The DLRM will be rescheduled if a quorum is not reached.

Voting members of the DLRM will include the Amgen Medical Monitor, the Amgen GSO or designated safety scientist, and all actively screening and enrolling investigators or their qualified sub-investigator designee. The team may recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower or higher 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. One or more dosing regimens may be selected based on clinical findings including safety, tolerability, and PK results from previous cohorts; after DLRT review, the DLRT may make recommendations for the next cohort dose and frequency. [redacted]. The Amgen Medical Monitor and GSO or designee and the majority (defined as greater than or equal to 50%) of actively screening and enrolling investigators participating in the DLRM must cast a positive vote indicating an acceptable safety profile was observed for AMG 994 to allow the dose level modification and/or cohort continuation/expansion to proceed. All available study data including demographics, medical history, concomitant medications,

AEs, ECGs, vital signs, laboratory results, and emerging PK or pharmacodynamics data will be reviewed. Data to be reviewed may be unqueried.

The dosing schedule is described by the Study Schema in the protocol synopsis (see Section 1.2).

Dose Cohort Stopping Rules

The DLRT will recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower or higher 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. One or more dosing regimens may be selected based on clinical findings including safety, tolerability, and PK results from previous cohorts; after DLRT review, the DLRT may make recommendations for the next cohort dose and frequency. [redacted] All available study data including demographics, medical history, concomitant medications, AEs, ECGs, vital signs, laboratory results, and emerging PK or pharmacodynamics data will be reviewed.

The Amgen Medical Monitor may suspend dosing and convene a DLRM at any time based on emerging safety data.

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

Dose-Limiting Toxicity

All events will be graded using the CTCAE version 5.0. The occurrence of any of the following events during the first or second DLT evaluation period will be considered a DLT, excluding events clearly related to disease progression or intercurrent illness:

- Any grade 5 event
- Grade 4 neutropenia or thrombocytopenia of any duration
- Grade 3 thrombocytopenia with clinically significant bleeding or lasting $>$ 7 days
- Febrile neutropenia
- Grade 4 anemia
- Grade 3 or 4 non-hematologic toxicity, with the following exceptions:
    - 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 grade 3 electrolyte abnormalities that last < 72 hours, are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions
- DLT Exemption: Grade 3 amylase or lipase elevations, as per CTCAE version 5.0, grade 4 elevations in amylase and lipase are defined as being associated with signs or symptoms of pancreatitis
- DLT Exemption: Other laboratory parameters of grade 3, not considered clinically relevant, and improved to grade ≤ 2 within 72 hours.

- Any grade 3 event requiring hospitalization
- 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, except for immune-mediated toxicities as outlined in Table 11-3 where a longer timeframe is specified
- Any other event requiring permanent discontinuation of AMG 994 (for example, as specified in Table 11-4, Infusion-Related Reactions)

The cumulative adverse event profile will be taken into consideration when making decisions on dose escalation and on any other dose-level or safety review.

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 ≥ 3 x ULN AND with serum TBL of > 2 x ULN without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities (see Section 6.2.3 for hepatotoxicity management and Section 11.7 for further explanation of Hy's law case and Management of Hepatic Function).

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

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

The DLT window (ie, DLT-evaluable period) during dose exploration will start on day 1 (start of the administration of the first infusion). The duration of the DLT windows and definition of DLT-evaluable subjects are shown below (Table 6-2).

All available safety data for subjects who are not DLT evaluable will still be evaluated and considered in DLRT recommendations.

A DLT will be defined as any of the events described above occurring in a subject during the DLT window excluding events clearly related to disease progression or intercurrent illness. The CTCAE version 5.0 (see Section 11.4) will be used to grade adverse events.

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

6.2.2.1 Dose Adjustment

A given subject should continue on the same dose level of AMG 994 throughout the study.

An exception to this may be considered when a given subject experiences a DLT or other intolerable AMG 994-related adverse event, but shows evidence of clinical benefit. The medical monitor and investigator, in consultation with the GSO, may deem it appropriate for such subjects to have a dose reduction to the immediate next lower dose. Each subject is only allowed 1 dose reduction.

No dose modifications for AMG 404 are recommended. Based on established preclinical and clinical data available from AMG 404 and other anti-PD1 therapies and

also on preclinical data from AMG 994, immune-mediated adverse reactions are expected to be associated to AMG 404 and emerging study safety data will inform any necessary revision of this initial expectation. Guidelines for withholding or discontinuing AMG 404 for immune-mediated reactions are listed in Table 11-3. If AMG 404 has been withheld, treatment with AMG 404 may be resumed after the adverse event (or associated signs/symptoms/laboratory parameters) has been reduced to grade ≤ 1 and corticosteroid has been tapered to prednisone < 10 mg or equivalent (per Table 11-3, myocarditis must be resolved to grade < 1).

6.2.2.2 Rules for Withholding or Restarting

- AMG 994, and AMG 404 if the subject is on combination therapy, should be withheld for any DLT or any adverse event that meets the criteria of a DLT but occurs outside of the DLT windows
- AMG 994, and AMG 404 if the subject is on combination therapy, should be withheld for potential hepatotoxicity as detailed in Table 11-2
- AMG 404 alone should be withheld for immune-mediated adverse reactions as detailed in Table 11-3
- AMG 994 and/or AMG 404 should be withheld for infusion-related reactions as specified in Table 11-4

For adverse events not addressed by Table 11-2, Table 11-3 and Table 11-4, AMG 994 and AMG 404 dosing can be resumed if the applicable event resolves to grade ≤ 1 or otherwise resolves to subject's baseline grade within 2 weeks. The restarting of therapy should be deemed appropriately safe by the investigator and Medical Monitor. For restart criteria following hepatotoxicity, immune-mediated reactions, and infusion-related reactions, refer to Table 11-2, Table 11-3 and Table 11-4, respectively. For immune-mediated hepatitis, if Table 11-2 and Table 11-3 are both applicable, Table 11-2 is to take precedence.

Subjects should not be restarted with AMG 994 and/or AMG 404 if the following treatment-related adverse events occur:

- Any grade 4 adverse events except those not considered DLT, OR
- Adverse event criteria are met for permanent withholding of AMG 994 and/or AMG 404 due to potential hepatotoxicity, immune-mediated reaction or infusion related reaction (Table 11-2, Table 11-3, or Table 11-4, respectively). For immune-mediated hepatitis, if Table 11-2 and Table 11-3 are both applicable, Table 11-2 is to take precedence.

If a subject experiences an adverse event meeting withholding or discontinuation criteria above from AMG 404, and if the subject is experiencing clinical benefit with AMG 994 monotherapy, a decision to have the subject continue with AMG 994 monotherapy alone, may be considered by the Amgen medical monitor in consultation with the investigator.

The reason for dose change of AMG 994 and/or AMG 404 is to be recorded on each subject's CRF.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

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

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 Modular IPIM.

6.4 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).

6.5 Treatment of Overdose

The effects of overdose of AMG 994 and AMG 404 are not known.

6.6 Prior and Concomitant Treatment

6.6.1 Prior Treatment

Prior therapies that were being taken/used from initial diagnosis through the time of consent will be collected.

6.6.2 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 the end of study.

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 Section 7.1, Section 7.2.1, and Section 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 and adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- 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 11.6 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

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will screen the subject in order to assess eligibility for participation. The screening window is up to 28 days prior to day 1.

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

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

Rescreen subjects must first be registered as screen failures and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28 day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days

after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (see Section 1.3). On-study visits may be completed within 1 day/week. The date of the first dose of AMG 994 or AMG 404 is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of AMG 994 and/or AMG 404 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, a safety follow-up visit will be performed at 30 (+7) days and 140 days (±1 week) after the last dose of protocol required therapies. These visits include adverse event/serious adverse event assessment, a physical exam, blood work (chemistry; coagulation; complete blood count [CBC]; adrenocortiocopic hormone [ACTH]; anti-neutrophil cytoplasmic antibodies [ANCA], anti-nuclear antibodies [ANA], pregnancy test), and urinalysis.

The chemistry includes albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN)/total urea, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein, thyroid stimulating hormone (TSH), and free T4.

8.1.4 Long-term Follow-up

Long-term follow-up phone call at 6 months (±1 week) after last dose of protocol required therapies to collect information on serious adverse events, survival, 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 through 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. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

8.2.1.5 Physical Measurements

Height [in centimeters] should be measured without shoes. Weight [in kilograms] should be measured without shoes.

8.2.1.6 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 11.9.

8.2.2 Efficacy Assessments

Tumor evaluations (by contrast-enhanced computed tomography [CT] or magnetic resonance imaging [MRI]) and tumor markers, if applicable, are to be collected at time points specified in the Schedule of Activities (see Section 1.3). Imaging may also be performed more frequently if clinically necessitated at the discretion of the managing physician.

All radiological imaging will be performed as indicated in the Site Imaging Manual provided by the central imaging core laboratory. In order to reduce radiation exposure for subjects, low dose CT should be utilized whenever possible.

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

All subjects must have MRI of the brain performed within 28 days prior to first dose of AMG 994. Subsequently, MRI brain scans may be performed at any time if subject has a history of CNS disease, or if signs or symptoms suggestive of central nervous system metastases are present. All brain scans on protocol are required to be MRI unless MRI is contraindicated, and then CT with contrast is acceptable.

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

Eligibility and determination of disease response for clinical management of subjects will be assessed at the clinical sites per Modified RECIST 1.1 (Section 11.11). Scans will be submitted to a central imaging core laboratory for archival and response assessment including Modified RECIST 1.1.

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

Radiographic response (Complete Response, Partial Response) requires confirmation by a repeat, consecutive scan at least 4 weeks after the first documentation of response and may be delayed until the next scheduled scan to avoid unnecessary procedures. Radiographic progression (Progressive Disease) requires confirmation by a repeat, consecutive assessment 4 to 6 weeks after the first detection of radiological progression. Upon discussion with the Sponsor, in the absence of clinical deterioration, subjects may continue to receive AMG 994 and AMG 404 combination treatment after confirmation of radiographic progressive disease as long as they continue to derive clinical benefit, until

clinical disease progression, or intolerance of study treatment, or clinically significant deterioration of health status requiring discontinuation, or the subject withdrawal of consent, whichever occurs first; or, in the absence of the above, up to 12 months if the subject achieves a complete response, and up to 24 months if partial response or stable disease.

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

8.2.3 Safety Assessments

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

8.2.3.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature. Subject must be in a rested and calm state for at least 5 minutes before blood pressure 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 CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF. Oxygen saturation will be measured using a standard pulse oximeter. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

8.2.3.2 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 (all 3 ECGs should be completed within a total of 5 minutes from the start of the first to the completion of the third), prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

- 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)
- Triplicate ECGs at time points after dosing

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

8.2.3.3 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.

8.2.4 Adverse Events and Serious Adverse Events

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

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

8.2.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the 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 first dose of protocol-required therapies through the end of study are reported using the Events CRF.

8.2.4.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through end of study visit are reported using the Events CRF.

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

Since the criteria for the CTCAE grading scale differs from the regulatory criteria for serious adverse events**, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as** grade 4 **without manifestation of life-threatening status)**, **it will be** left to the investigator's judgment to **also** report these abnormalities as serious adverse events. **For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.**

8.2.4.1.3 Serious Adverse Events After the Protocol-required Reporting Period

If the investigator becomes aware **of** serious adverse events **suspected to be related to the investigational product after** the protocol-required reporting period (as defined in Section 11.4) **is complete, then** these serious adverse events **will** be reported to Amgen within 24 hours following the investigator's awareness of the event.

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

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

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

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

8.2.4.2 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.

8.2.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

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

8.2.4.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

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

8.2.4.5 Safety Monitoring Plan

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

8.2.4.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until 6 months **(for female subjects)** or 8 months **(for female partners of male subjects)** after the last dose of protocol required therapies.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

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

Further details regarding pregnancy and lactation are provided in Section 11.5.

8.2.5 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.

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

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (see Section 1.3).

Pregnancy Testing

A highly sensitive serum pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a

male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional pregnancy testing should be performed at monthly intervals during treatment with protocol-required therapies and at the 30 day and 140 day follow-up visit

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

8.2.6 Pharmacokinetic Assessments

All subjects enrolled will have pharmacokinetic samples assessed.

Blood samples of approximately 5 and 3 mL will be collected for measurement of serum concentrations of AMG 994 and AMG 404, respectively as specified in the Schedule of Activities (Section 1.3). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.2.7 Pharmacodynamic Assessments

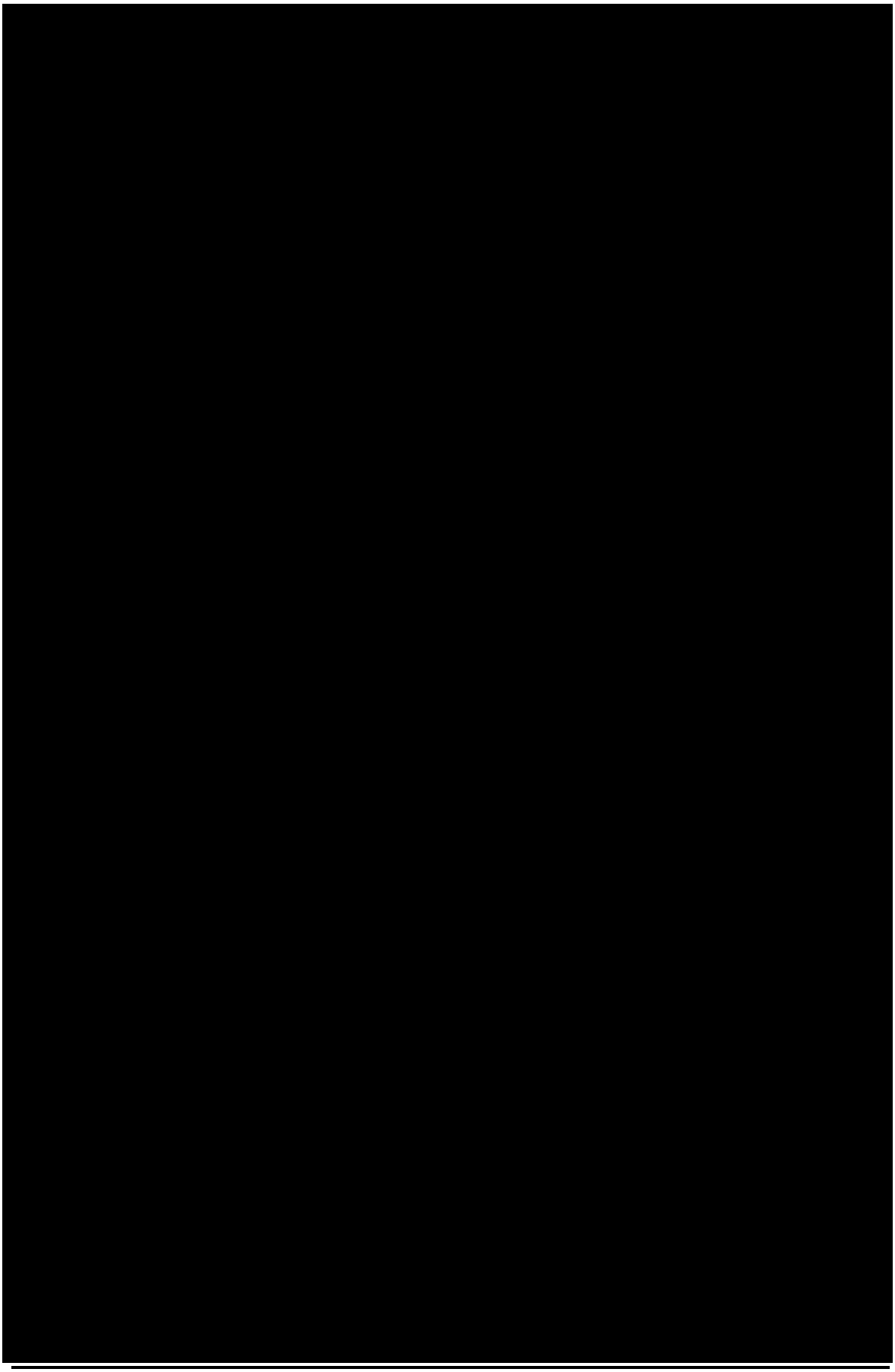
Biopsy tissue will be collected for evaluation of pharmacodynamic changes as specified in the Schedule of Activities (Section 1.3).

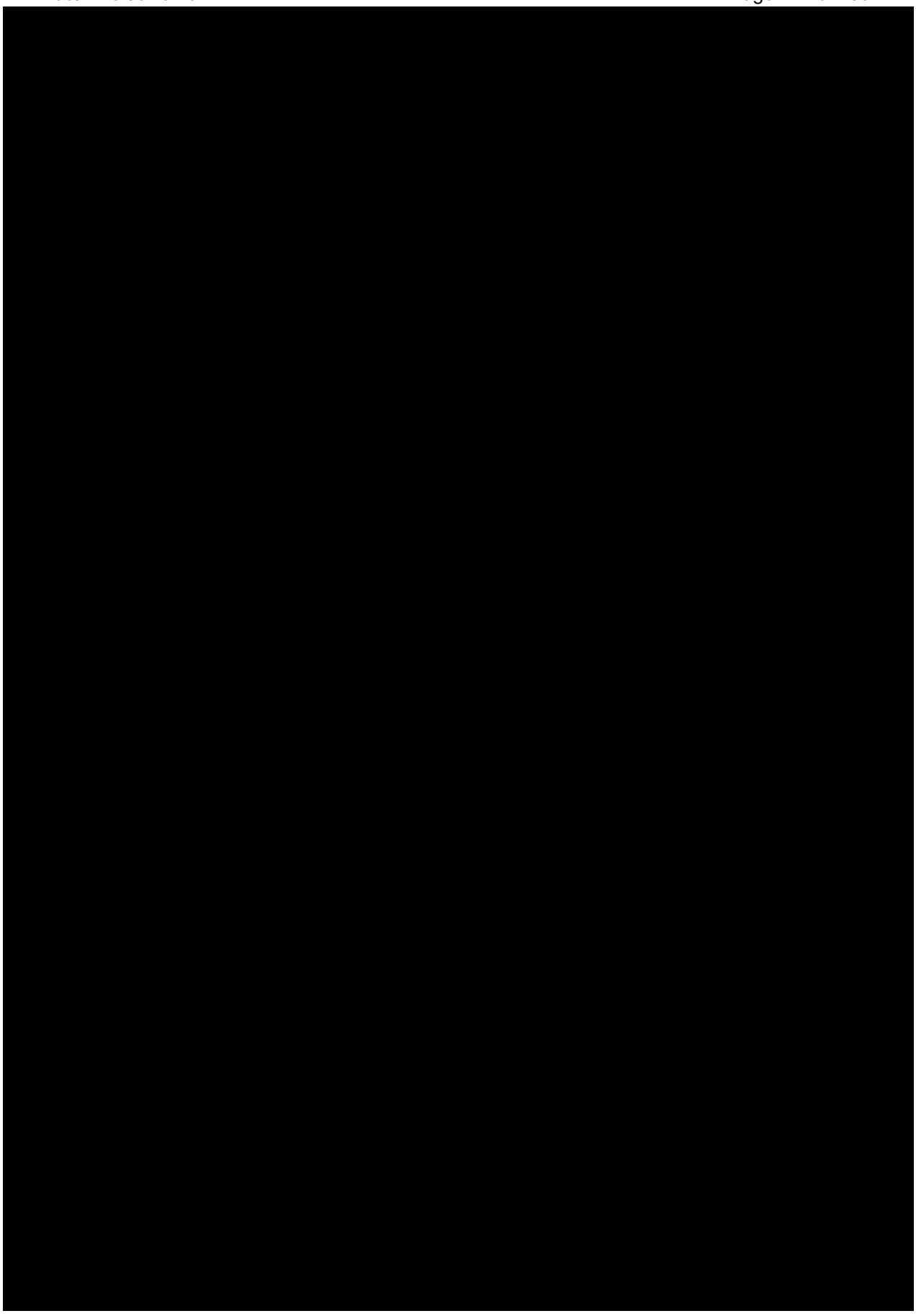
8.2.8 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of advanced solid tumors and/or to identify subjects who may have positive or negative response to AMG 994 and AMG 404 combination therapy. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

The final disposition of samples will be described in Section 11.6.

[redacted]





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 214 subjects will be enrolled in this study. Approximately 94 subjects will be enrolled in the dose-exploration cohorts (Part 1). Up to 120 subjects will be enrolled in the dose-expansion cohorts (Part 2), 30 subjects in each of 4 tumor types (mesothelioma, NSCLC squamous cell carcinoma and adenocarcinoma [if upon screening found to be MSLN positive], pancreatic adenocarcinoma, and high grade serous ovarian carcinoma).

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/MTCD. 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 cohorts, a total subject sample size of 120 will provide a 91% probability of observing at least 1 adverse event with 2% incidence rate. An exact 95% binomial CI will be provided for overall response rate. With the 30 subjects in a cohort of subjects with a particular tumor type and a 20% overall response rate, the expected 95% CI would be 8% to 39%. 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, [redacted] 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 994 or AMG 404.

The analysis of DLT in the initial safety review period [redacted] will be conducted on the Early DLT Analysis set defined as all subjects that are enrolled and receive at least 1 dose of AMG 994 with an evaluable early DLT endpoint (evaluable in AMG 994 monotherapy cohort per Table 6-2).

The analysis of DLT in the cumulative safety review period will be conducted on the Cumulative DLT Analysis set defined as all subjects that are enrolled and receive at least 1 dose of AMG 994 or AMG 404 with an evaluable cumulative DLT endpoint (experience a DLT during monotherapy cohort or evaluable in combination therapy cohort per Table 6-2).

The analysis of objective response will be conducted on the Efficacy Evaluable Analysis set defined as all subjects that are enrolled to a dose expansion cohort and receive at least 1 dose of AMG 994 or AMG 404 with at least 1 tumor lesion that is measurable in contrast-enhanced CT as defined by modified RECIST 1.1, with the following exceptions. The following subjects will be excluded from the Efficacy 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.

[redacted]

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 safety data, 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 2 of the same grade 4 adverse events) at least possibly related to AMG 994 or AMG 404, further accrual will be suspended; Amgen will conduct a safety analysis and submit to the regulatory authority for review prior to resuming enrollment.

Given that a fixed-dose administration of AMG 404 [redacted] is used as part of the AMG 994 plus AMG 404 combination, the 2-parameter BLRM for single agent AMG 994 will be used. 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) = [redacted], SD of “a” SD(ln(a)) = [redacted], mean ln(b) = [redacted], SD(ln(b)) = [redacted] and correlation = [redacted] The target toxicity probability interval (TPI) is defined as a rate at least [redacted] and less than [redacted]; an excessive or unacceptable TPI is a rate of [redacted] or higher. The prior distribution is specified such that probability of DLT is [redacted] for the starting dose [redacted] and [redacted] for the reference dose [redacted] where the probability that the true DLT rate is [redacted] at the lowest planned dose is [redacted] and the probability the true DLT rate is [redacted] at the reference dose is [redacted]. The BLRM will be used [redacted] to recommend the next dose level and at the end of dose

exploration the recommended MTD will be the level with the highest probability of the target TPI, but with a less than [redacted] probability of an excessive or unacceptable TPI.

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

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 1 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 ≥ 80% that the true grade 4 or higher treatment-related adverse event rate is ≥ 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
20	≥ 6
40	≥ 11
60	≥ 15
80	≥ 20
100	≥ 24
120	Dose Expansion Complete

Table 9-2. Operating Characteristics With Batch Size of 20 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	1.2%	118.8
0.15	9.6%	111.5
0.20	37.6%	90.1
0.25	76.0%	59.9
0.30	95.7%	38.0

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 Efficacy Analysis Set, the proportion of subjects and 95% CL with an objective response (complete or partial response per modified RECIST 1.1) will be tabulated by tumor type and planned dose level and schedule. For all subjects in the Efficacy 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 response (DOR, per modified RECIST 1.1); 2) overall survival (OS); 3) progression-free survival (PFS, per modified RECIST 1.1); 4) time to progression (TTP, per modified RECIST 1.1) and 5) time to subsequent therapy. Kaplan-Meier methods will be used to estimate appropriate landmarks for DOR, OS, PFS and TTP (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 994 or AMG 404. The

	analysis of early DLTs will be conducted on the Early DLT Analysis Set and the analysis of cumulative DLTs will be conducted on the Cumulative DLT Analysis Set. Subject incidence of both early and cumulative DLT will be tabulated by planned dose level. A table of both early and cumulative DLTs will be provided. The probability of a subject having an early and cumulative DLT by dose level will be estimated using a 2-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.

[redacted]

9.4.2.3.8 Exposure to Investigational Product

Details of AMG 994 and AMG 404 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

The PK parameters of AMG 994 and AMG 404 including, but not limited to, C_{max}, t_{max}, and AUC will be estimated using non-compartmental methods and summarized by dose level using means, geometric means, standard deviations, coefficients of variation, medians, minimums, and maximums. Individual concentration-time profiles will be summarized by dose level. Serum AMG 994 and AMG 404 concentrations at each time point along with PK parameter values may be listed for each subject. Summary statistics will be computed for each sampling time and parameter as appropriate. The relationship between AMG 994 exposure and efficacy/safety may be conducted.

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
ADR	adverse drug reaction
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ANCA	anti-neutrophil cytoplasmic antibodies
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}14d}$	AUC from 0 to 14 days postdose
$AUC_{0\text{-}28d}$	AUC from 0 to 28 days postdose
BLRM	Bayesian Logistics Regression Model
BUN	blood urea nitrogen
CD40	cluster of differentiation 40
CD40L	CD40 trimeric ligand
CH2	heavy chain constant domain 2
CFR	U.S. Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum concentration
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
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.
Exposure-Response Analysis	mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic (PK) exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic effects, efficacy and safety endpoints.
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
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HC	Heavy chain
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation

ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IHC	immunohistochemistry
Il	interleukin
IND	Investigational New Drug
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
[redacted]	
K_d	equilibrium dissociation constant
KPS	Karnofsky Performance Status
Lansky PFS	Lansky Play-Performance Scale
LC	light chain
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MRI	magnetic resonance imaging
MSLN	mesothelin
MTD/MTCD	maximum tolerated dose/maximum tolerated combination dose
MUGA scan	multigated acquisition scan
NCT	National Clinical Trials
NSCLC	nonsmall-cell lung cancer
OR	objective response
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PK	Pharmacokinetics
PR	partial response

RO	receptor occupancy
SAT	safety assessment team
scFv	single chain variable fragments
SEFL2	stable effector functionless
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
TMF	trial master file
TPI	toxicity probability interval
TSH	thyroid stimulating hormone
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
WOCBP	women of childbearing potential

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the central laboratory and/or by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.1 to Section 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 Potassium Chloride Total protein Albumin Calcium Glucose BUN or Urea Creatinine Total bilirubin ALP AST (SGOT) ALT (SGPT) TSH Free T4	PT/INR PTT/APTT Fibrinogen Fibrin split products D-dimer	Specific gravity pH Blood Protein Glucose Bilirubin WBC RBC Epithelial cells Bacteria Casts Crystals	RBC Nucleated RBC Hemoglobin Hematocrit MCV MCH MCHC RDW Reticulocytes Platelets WBC Differential • Total neutrophils • Segmented neutrophils • Bands/stabs • Eosinophils • Basophils • Lymphocytes • Monocytes • Myeloblasts • Promyelocytes • Myelocytes • Metamyelocytes • Atypical lymphocytes	<u>Central Laboratory</u>: [redacted] Tumor biopsy[a] SP74 Ventana MSLN IHC assay[b] AMG 994 and AMG 404 Pharmacokinetic Assessments <u>Local Laboratory</u>: Hep B surface antigen Hep C antibody HIV[c] Serum Pregnancy ACTH ANA ANCA (cytoplasmic and perinuclear)

[a] Archived tumor tissue acceptable for the screening sample only.

[b] NSCLC squamous cell carcinoma and adenocarcinoma patients only, Part 2 only.

[c] HIV assessment is required.

ACTH = adrenocorticotropic hormone; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IHC = immunohistochemistry; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin;

MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MSLN = mesothelin; 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; TSH = thyroid stimulating hormone; WBC = white blood cell count

11.3 Appendix 3. Study Governance Considerations

Committee(s)

Dose Level Review Meetings (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. If a Site Investigator does this, the Site Investigator must provide written agreement with the designee or delegate's vote.

For a DLRM to occur, the Medical Monitor must attend, and the GSO or delegate must attend. In addition, a quorum of Site Investigators must be present. A quorum is defined as 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, 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 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. 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 Council for 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.

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.

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 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.

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

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the SAP.

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

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

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
• The investigator will then record all relevant adverse event/serious adverse event information in the Event 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);
  ○ Did the event start prior to first dose of investigational product, other protocol-required therapies;
  ○ Assessment of seriousness;
  ○ Severity (or toxicity defined below);
  ○ Assessment of relatedness to investigational product or other protocol-required therapies and/or study-mandated activity and/or procedures;
  ○ Action taken; and
  ○ Outcome of event.

- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event 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, and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.

- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

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

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

- The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system.
- If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using a paper based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event (eSAE) Contingency Report Form) (see Figure 11-1) within 24 hours of the investigator's 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 system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 11-1).
- Once the study has ended, serious adverse event(s) **suspected to be related to investigational product will** be reported to Amgen if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

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

A Study # 20190136 AMG 994 and AMG 404	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day_____ Month____ Year_____

Serious Adverse Event diagnosis or syndrome **If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report** *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP	**Is event serious?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?				**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						AMG 994		AMG 404			
						No✓	Yes✓	No✓	Yes✓		
				☐ Yes ☐ No							
				☐ Yes ☐ No							
				☐ Yes ☐ No							

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

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

Date Admitted Day Month Year	**Date Discharged** Day Month Year

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

IP/Amgen Device:		**Date of Initial Dose** Day Month Year	**Date of Dose** Day Month Year	**Prior to, or at time of Event** **Dose**	**Route**	**Frequency**	**Action Taken with Product** 01 Still being Administered 02 Permanently discontinued 03 Withheld	**Lot # and Serial #**
Amgen IP/IMP: AMG 994	☑ Open Label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Amgen IP/IMP: AMG 404	☑ Open Label							Lot # _____ ☐ Unknown Serial # _____

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A Study # 20190136 AMG 994 and AMG 404	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

☐ Unavailable / Unknown

Site Number	Subject ID Number

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

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

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

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

Test												
Unit												
Date (Day Month Year)												

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

Date (Day Month Year)	Additional Tests	Results	Units

A Study # 20190136 AMG 994 and AMG 404	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

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

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

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

Male and female subjects of childbearing potential should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant or father a child during treatment and for 6 months (**for** female **subjects**) or 8 months (**for female partners of** male **subjects**) after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

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

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 8 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 6 months after the last dose of protocol-required therapies
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of 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 through6 months after the last dose of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or 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).

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 8 months after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed 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 6 months after discontinuing protocol-required therapies.
- 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 219.
- 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 6 months after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20190136 (Amgen Investigational Products: AMG 994 and AMG 404) (open label)

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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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: 20190136 (Amgen Investigational Products: AMG 994 and AMG 404) (open label)

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(s)	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

11.6 Appendix 6. Sample Storage and Destruction

Any blood biomarker, pharmacokinetics (PK), and biopsy sample collected according to the Schedule of Activities (Section 1.3) 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 994, 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.

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

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

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

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

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

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

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

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

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

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

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

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 11-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate 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 11.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 11-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

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

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

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

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels

- A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

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

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

11.8 Appendix 8. Protocol-specific Anticipated Serious Adverse Events

Anticipated serious adverse events are events that are anticipated to occur in the study population at some frequency independent of investigational product exposure and do not need to be reported individually as an FDA IND safety report by the sponsor. Identification and reporting of anticipated serious adverse events is the responsibility of the sponsor; the investigator is responsible for reporting adverse events and serious adverse events as described in Appendix 11.4.

Anticipated Serious Adverse Events for Study 20190136

Preferred Term[1]
N/A

[1] MedDRA Version 22.1

11.9 Appendix 9. ECOG Performance Status and NYHA Classification

Eastern Cooperative Oncology Group Performance Status 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
ECOG = Eastern Cooperative Oncology Group

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.

11.10 Appendix 10. Toxicity Management Guidelines

Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Pneumonitis	Grade 2 (symptomatic, involves more than 1 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) OR Grade 2 recurrent	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 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 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		

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Footnotes defined on last page of this table

Table11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Hepatitis	Grade 2 (asymptomatic, AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN [for patients with values < ULN at baseline])	Withhold	Administer corticosteroids at an initial dose of 0.5 to 1 mg/kg/d prednisone (or equivalent) followed by taper.	Monitor with liver function tests more frequently until returned to baseline or stable.
	Grade 3 (symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis [AST or ALT 5-20 x ULN and/or total bilirubin 3-10 x ULN])	Permanently discontinue	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider mycophenolate mofetil if refractory to corticosteroids or no improvement after 3 days.	
	Grade 4 (decompensated liver function eg, ascites, coagulopathy, encephalopathy, coma [AST or ALT > 20 x ULN and/or total bilirubin > 10 x ULN])		Administer corticosteroids at an initial dose of 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider mycophenolate mofetil if refractory to corticosteroids or no improvement after 3 days.	

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Footnotes defined on last page of this table

Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Hypophysitis	Grade 3 or 4 not responsive to therapy within 2 days	Permanently discontinue	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 not responsive to therapy within 2 days	Permanently discontinue	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 not responsive to therapy within 2 days	Permanently discontinue	Initiate thyroid hormone supplementation.	Monitor subjects for signs and symptoms of hypothyroidism. Consider endocrine consultation.
Hyperthyroidism	Grade 3 or 4 not responsive to therapy within 2 days	Permanently discontinue	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 potassium iodide (SSKI)	Monitor subjects for signs and symptoms of hyperthyroidism. Consider endocrine consultation.

			or thionamide (methimazole or propylthiouracil [PTU]).	

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Footnotes defined on last page of this table

Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Diabetes Mellitus	Grade 3 not responsive to therapy within 2 days	Permanently discontinue	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) lasting greater than 3 days	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)			

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Footnotes defined on last page of this table

Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 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	Any Grade (if immune related)	Permanently discontinue	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.

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Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 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		

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Footnotes defined on last page of this table

Table 11-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Reactions Associated With AMG 404*

Immune-related Adverse Reactions	Severity (CTCAE Grade Version 5.0 or Specific Conditions)	AMG 404 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)			

- General considerations:
- 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 404 has been withheld, treatment with AMG 404 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.

ACTH = adrenocorticotropic hormone; ADL = activities of daily living; ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; CSF = cerebrospinal fluid; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; GI = gastrointestinal; IV = intravenous; MRI = magnetic resonance imaging; PTU = propylthiouracil; SSKI = potassium iodide; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

* *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 (Brahmer et al, 2018)*

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Table 11-4. Management of Infusion-related Reactions With AMG 994 or AMG 404

Severity (CTCAE Grade Version 5.0)	AMG 404 or AMG 994 Dose Modification	Management	Premedication at Subsequent Dosing
Grade 1 (mild transient reaction; infusion interruption not indicated; intervention not indicated)	Interrupt AMG 404 or AMG 994 or slow the rate of the infusion to 50% or less of the standard rate.	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • If the infusion is interrupted, then after all symptoms have resolved, consider rechallenge with a reduced infusion rate (50% or less of standard rate) and additional premedication (such as corticosteroids and antihistamines). • Treat per institutional guidelines.	None
Grade 2 (therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours)	Interrupt AMG 404 or AMG 994 or slow the rate of the infusion. For subjects who develop grade 2 infusion-related reaction despite adequate premedication, permanently discontinue AMG 404 or AMG 994.	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • If the infusion is interrupted, then after all symptoms have resolved, consider rechallenge with a reduced infusion rate (50% or less of standard rate) and additional premedication (such as corticosteroids and antihistamines). • Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, and narcotics.	Subject may be premedicated 1.5 hours (± 30 minutes) prior to infusion of AMG 994 or AMG 404 with: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).

Grade 3 (prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae) OR Grade 4 (life-threatening consequences; urgent intervention indicated)	Permanently discontinue study drug.	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Hospitalization may be indicated. • 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. In cases of anaphylaxis, epinephrine should be used immediately.	No subsequent dosing

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAIDS = nonsteroidal anti-inflammatory drugs.

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**

  1 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.

  2 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).

  3 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**

  4 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.

  5 Other examples of non-measurable lesions include:

    - Lesions with prior local treatment: tumor lesions situated in a previously irradiated area, or an area subject to other loco-regional therapy, should not be considered measurable unless there has been demonstrated progression in the lesion.
    - Biopsied lesions
    - Categorially, clusters of small lesions, bone lesions, inflammatory breast disease, and leptomeningeal disease are non-measurable.

Methods of Measurement

- **Measurement of Lesions** - The longest diameter of selected lesions should be measured in the plane in which the images were acquired (axial plane). All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 4 weeks before study Day 1.
- **Methods of Assessment** - The same method of assessment and the same technique should be used to characterize each identified and reported lesion throughout the trial.
- **CT/MRI** – Contrast-enhanced CT or MRI should be used to assess all lesions. Optimal visualization and measurement of metastasis in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. CT and MRI should be performed with ≤ 5 mm thick contiguous slices.

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

- **Target Lesions** - All measurable lesions up to a maximum of five (5) lesions per organ and ten (10) lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
  - Target lesions should be selected on the basis of their size (lesions with the longest diameter) and suitability for accurate repeated measurements.
  - Pathologic lymph nodes (with short axis ≥ 15 mm) may be identified as target lesions. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference by which to characterize objective tumor response.

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

Response Criteria

Evaluation of Target Lesions

* Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
* Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
* Progressive Disease (PD):	At least a relative 20% increase and an absolute increase of 5 mm in the sum of the diameters of target lesions, taking as reference the smallest sum on study, or the appearance of one or more new lesions.
* Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters since the treatment started.

Evaluation of Non-target Lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
* Progressive Disease (PD):	Unequivocal progression of existing non-target lesions and/or appearance of one or more new lesions.[1]

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

Evaluation of Overall Response

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

In general, the subject's best response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

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

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

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

Time Point Response: Subjects with Non-Target Disease Only

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

‡ "Non-CR/non-PD" is preferred over "SD" for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Overall Response: Confirmation of Complete Response (CR) and Partial Response (PR) required

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

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

Special Notes on Response Assessment

- Nodal lesions – Lymph nodes identified as target lesions should always have the actual short axis measurement recorded, even if the nodes regress to below 10 mm on study. In order to qualify for CR, each node must achieve a short axis < 10 mm, NOT total disappearance. Nodal target lesion short axis measurements are added together with target lesion' longest diameter measurements to create the sum of target lesion diameters for a particular assessment (timepoint).
- Target lesions that become "too small to measure" – While on study, all lesions (nodal and non-nodal) recorded at baseline should have their measurements recorded at each subsequent evaluation. If a lesion becomes less than 5 mm, the accuracy of the measurement becomes reduced. Therefore, lesions less than 5 mm are considered as being "too small to measure," and are not measured. With this designation, they are assigned a default measurement of 5 mm. No lesion measurement less than 5 mm should be recorded, unless a lesion totally disappears and "0" can be recorded for the measurement.

- New lesions – The term "new lesion" always refers to the presence of a new finding that is definitely tumor. New findings that only may be tumor, but may be benign (infection, inflammation, etc.) are not selected as new lesions, until that time when the review is certain they represent tumor.
  - If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
  - A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression, regardless of any response that may be seen in target or non-target lesions present from baseline.
- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression with an additional imaging assessment even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from scar or normal tissue. When the evaluation of complete response (CR) depends on this determination, the residual lesion may be further investigated by additional scans to be discussed with Sponsor, 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.

Amendment 4

Protocol Title: A Phase 1, Multicenter, Open-label, Dose Exploration and Dose Expansion Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 994 Monotherapy and Combination of AMG 994 and AMG 404 in Subjects with Advanced Solid Tumors

Amgen Protocol Number: AMG 994 and AMG 404, 20190136

EudraCT Number: 2020-003937-40

NCT Number: NCT04727554

Amendment Date: 16 June 2022

Rationale:

This protocol is being amended to update long-term follow-up (LTFU) safety reporting language in accordance with Amgen processes for ongoing interventional studies with a LTFU period. Changes including, but not limited to, the following were incorporated into the protocol:

- Added language to schedule of activities (SoA) to clarify that after end of study, serious adverse events suspected to be related to investigational product need to be reported to Amgen if the investigator becomes aware of the event.
- Language in serious adverse events section was added to clarify that it is up to the investigator's judgment to report grade 4 abnormalities by Common Terminology Criteria for Adverse Events (CTCAE) as serious adverse events, and that comprehensive documentation of the event severity must be recorded in the subject medical record.
- Updated product complaints language to make clear that all components distributed with the drugs can be included in communications with regard to product complaints; and to clarify that AMG 994 and AMG 404 are the investigational products provisioned and/or repackaged/modified by Amgen.
- Updated language in adverse events and serious adverse events section to maintain consistency with clinical trial (CT) protocol template language.

- Language in serious adverse events after the protocol-required reporting period section was updated to clarify that all serious adverse events suspected to be related to the investigational product needs to be reported to Amgen within 24 hours following the investigator's awareness of the event; investigators need to collect/report fatal serious adverse events (regardless of causality) to Amgen within 24 hours following the investigator's awareness of the event; that there is no requirement to actively monitor study subjects after end of study (EOS), this in regard to study subject treatment by the investigator; and to clarify that additional information may need to be collected from the subject's records after the subject EOS, that if further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event.
- Updated pregnancy and lactation language to clarify that details on all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected until 6 months or 8 months, respectively.
- Language in Appendix 4 was added to clarify that SAE suspected to be related to investigational products will be reported to Amgen if the investigator becomes aware of a serious adverse event.
- Updated Appendix 5 pregnancy and lactation section to clarify language on the pregnancy prevention requirements and the potential risk to the fetus if the female subjects or female partners of male subjects become pregnant 6 months or 8 months, respectively, after the last dose of protocol-required therapies.
- Administrative and editorial changes including typographical, grammatical, and formatting have been made throughout the protocol for clarification.

Amendment 3

Protocol Title: A Phase 1, Multicenter, Open-label, Dose Exploration and Dose Expansion Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 994 Monotherapy and Combination of AMG 994 and AMG 404 in Subjects with Advanced Solid Tumors

Amgen Protocol Number AMG 994 and AMG 404, 20190136

EudraCT number 2020-003937-40

NCT number: TBD

Amendment Date: 03 December 2020

Rationale:

This protocol is being amended to address feedback from the Food and Drug Administration (FDA) during the pre-Investigational New Drug meeting to expand the inclusion criterion related to renal function, allowing enrollment of subjects with moderate renal impairment. Additional clarifications and updates are being made to the Schedule of Activities (SOA) tables to ensure all activities are accurately reflected within the tables and the associated footnotes. The following changes were incorporated into the study:

- Inclusion criterion 111 has been updated to allow subjects with moderate renal impairment to be enrolled into the study.
- The SOA tables were updated to more accurately and more clearly reflect the timepoints for vital sign collection and ensure consistency with the associated footnotes.
- End of Infusion safety laboratory collections were added (hematology, chemistry, and coagulation tests) to all cohorts in the Dose Exploration SOA tables.

- Updated timing and number of electrocardiogram (ECG) assessments to include consistent timepoints for ECGs to allow/enable monitoring of patient cardiac safety at appropriate timepoints during the first few cycles of therapy.
- Schedule of Assessments Table 1-3 was reformatted to show all timepoint collections more accurately.
- Biopsy samples were deleted from the Dose Exploration and Dose Expansion SOA tables at the End of Treatment timepoints as they will not be collected.
- Updated language in Section 8.2.2 related to continuation of AMG 994 and AMG 404 combination treatment after confirmation of disease progression to be consistent with Section 4.
- Standard deviation calculations for the Bayesian Logistic Regression Model were update in Section 9.4.1.1.

Amendment 2

Protocol Title: A Phase 1, Multicenter, Open-label, Dose Exploration and Dose Expansion Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 994 Monotherapy and Combination of AMG 994 and AMG 404 in Subjects with Advanced Solid Tumors

Amgen Protocol Number AMG 994 and AMG 404 20190136

Amendment Date: 22 October 2020

Rationale:

This protocol is being amended to:

- Update protocol to reflect Adverse Event collection from first dose of protocol required therapies through end of study.
- Update protocol to accurately reflect collection of Serious Adverse Event information and performance of Concomitant Medication Review from screening through end of study.
- Update protocol to correctly reflect intended coagulation, hematology, and chemistry assessments.
- Delete duplicated exclusion criterion related to male subjects with female partners of reproductive potential and renumbered accordingly.
- Updated inclusion/exclusion criteria numbering to coincide with numbering used in study database and case report forms.
- Update exclusion criterion 208 to align with requirements for AMG 404 by adding "[redacted]
- Revise the number/frequency of Whole Blood for Cytometry samples required for the study.
- Update the protocol to provide a window for tumor evaluation scans.
- Revise the protocol to further clarify the hospitalization requirements for the study.
- [redacted]

[redacted] accurately reflect Hep B surface antigen, Hep C antibody, and HIV as local laboratory tests; clarify that HIV testing is a required test; and clarify that IHC testing for NSCLC patients is only required in Part 2 of the study.

- Administrative, typographical and formatting changes were made throughout the protocol. Updates to safety language have been implemented throughout the protocol to align with the current template.

Amendment 1

Protocol Title: A Phase 1, Multicenter, Open-label, Dose Exploration and Dose Expansion Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 994 Monotherapy and Combination of AMG 994 and AMG 404 in Subjects with Advanced Solid Tumors

Amgen Protocol Number (AMG 994 and AMG 404) 20190136

EudraCT Number 2020-003937-40

Amendment Date: 14 October 2020

Rationale:

This protocol is being amended to include changes as described in Amgen's response to Food and Drug Administration's 23 September 2020 information request. Changes include:

- Remove "…in the investigator's opinion, standard therapy does not exist" from Inclusion Criteria language
- Modify the dose limiting toxicity (DLT) definition to remove the criterion that "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."
- Update dose modification and discontinuation guidelines to provide clarity and consistency
- Revise Exclusion Criteria to clarify that patients with sarcomatoid mesothelioma and small cell lung cancer will not be enrolled into Study 20190136
- Clarify and correct discrepancies in the protocol regarding the enrollment of patients with squamous non-small cell lung cancer (NSCLC) who express mesothelin (MSLN) into Part 2 of the study
- Add MSLN (SP74) Ventana immunohistochemistry (IHC) assay to assess mesothelin expression in patients with squamous NSCLC during dose expansion
- Delete Table 6-2 to ensure consistency throughout the protocol on management of adverse events of AMG 404 and AMG 994
- Revise Dose Modification and Discontinuation Guidelines for AMG 404
- Revise Toxicity Management Guidelines for both AMG 994 and AMG 404
- Remove the Amgen Standard Grading Scale that had previously been inadvertently included in the protocol