Title Page

Protocol Title:		A Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 404, a Programmed Death-1 (PD-1) Antibody, [redacted], in Patients With Advanced Solid Tumors
Short Protocol Title:		AMG 404 in Patients with Advanced Solid Tumors
Protocol Number:		20180143
Investigational Product:		AMG 404
Trade Name:		Not applicable
Sponsor	**Name of Sponsor:**	Amgen Inc.
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EudraCT Number:		2018-004268-80
NCT Number:		**NCT03853109**
Protocol Date:		**Document Version** — **Date** Original — 23 October 2018 Amendment 1 — 02 January 2019 Amendment 2 — 15 July 2019 Amendment 3 — 31 January 2020 Amendment 4 — 24 November 2020 Amendment 5 — 16 July 2021 **Amendment 6 — 20 May 2022**
Version/Date:		**Data Element Standards Version** 6.1

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 404, a Programmed Death-1 (PD-1) Antibody, [redacted], in Patients With Advanced Solid Tumors, dated **20 May 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 and dependent children) and my sub-investigators (including, if applicable, their spouses and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

1. Table of Contents

[redacted]

[redacted]

[redacted]

[redacted]

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2. Protocol Synopsis

Protocol Title: A Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 404, a Programmed Death-1 (PD-1) Antibody, [redacted], in Patients With Advanced Solid Tumors

Short Protocol Title: AMG 404 in Patients with Advanced Solid Tumors

Study Phase: 1

Indication: Advanced solid tumors

Rationale

The programmed cell death-1 (PD-1) receptor-ligand interaction is a major pathway that tumors use to suppress immune control. PD-1, part of the immunoglobulin (Ig) superfamily and related to CD28 and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).

Enhancement of anti-tumor immunity through inhibition of PD-1 has been effective in treatment of many malignancies when given as a single agent and when given as part of combination therapies. AMG 404, the investigational product under study, is a monoclonal antibody that binds to PD-1 and blocks its ability to interact with ligands PD-L1 and PD-L2.

This first in human AMG 404 study is designed to assess safety and tolerability of AMG 404 monotherapy, [redacted] in patients with solid tumor malignancies.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability and determine the recommended phase 2 dose (RP2D) of AMG 404 in patients with advanced solid tumors	• Dose limiting toxicities (DLTs), treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, and clinical laboratory tests
[redacted]	
Secondary	
• To evaluate the pharmacokinetics (PK) of AMG 404 as a monotherapy [redacted]	• PK parameters of AMG 404 including, but not limited to, maximum observed serum concentration (C_{max}), time to achieve C_{max} (t_{max}), and area under the serum concentration-time curve (AUC)
• To assess the immunogenicity of AMG 404 as a monotherapy [redacted]	• Subject incidence of anti-AMG 404 antibodies
• To evaluate the preliminary antitumor activity of AMG 404 as a monotherapy [redacted]	• Objective tumor response, duration of overall response, progression-free survival, disease control rate (DCR), and duration of stable disease measured by CT/MRI and assessed per modified RECIST 1.1

Hypotheses

AMG 404 is safe and well tolerated in patients with advanced solid tumors.

Overall Design

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics of AMG 404 as a monotherapy [redacted], in subjects with advanced solid tumors. The study may be conducted in Australia, United States, France, Poland, Spain, Turkey, United Kingdom, Belgium, South Korea, Taiwan, Japan, China, Singapore, Canada, Brazil, and Mexico. Other countries or regions may participate. [redacted]. Cohorts 1-9 will evaluate the safety, tolerability, PK and pharmacodynamics of AMG 404 with the following Q4W doses: Cohort 1 – 240 mg, Cohort 2 – 480 mg, Cohort 3 – Expansion at the dose of 480 mg (subjects enrolled outside of China), Cohort 4 – Exploratory Dose of 1050 mg, Cohort 5 – China and National Medical Products Administration (NMPA) certified sites in Taiwan and/or Hong Kong Specific Expansion at the recommended phase 2 dose (RP2D) with a safety lead-in [redacted] Cohort 6 – Expansion at the RP2D , Cohort 7 – Expansion at the RP2D in specific indications as specified in Section 3.1, Cohort 8 – Expansion at the RP2D in subjects with tumors that are microsatellite instability-high (MSI-H) or mismatch repair deficient

(dMMR), and Cohort 9 – Expansion at the RP2D in subjects with non-small cell lung cancer (NSCLC) that is PD-L1 positive, Tumor Proportion Score (TPS) ≥ 50% (Cohorts 6-9 will enroll subjects outside of China).

In Cohorts 1-9, AMG 404 will be administered intravenously (IV) over approximately 30 minutes, every 4 weeks in subjects with advanced solid tumors. Cohorts 3 and 4 can be opened once Cohort 2 has been completed and determined to be tolerable. Cohorts 5-9 can be opened once the first 6-9 subjects in Cohort 4 have completed the DLT evaluation period and data have been reviewed to determine the RP2D. The DLT evaluation period will be 28 days. The Dose Level Review Meeting (DLRM) may recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), continuation or delay in dosing, repetition or expansion of a cohort, de-escalation to a lower dose, or termination of the study. Administration of AMG 404 (in all cohorts) 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. Subjects with complete response may **be permitted to** continue treatment beyond 12 months, up to a maximum of 24 months of total therapy, **upon discussion with** the medical monitor. **Subjects with complete response, partial response, stable disease or continued clinical benefit at 24 months of treatment, may continue treatment for up to an additional 24 months (up to 48 months of treatment in total), upon discussion with the medical monitor.** If a subject completes or discontinues treatment for reasons other than progression, tumor evaluations should continue according to the Schedule of Activities (Table 3-1) until progression or start of a new treatment regimen.

Cohorts 1, 2 and Cohort 4

The doses of 240 mg, 480 mg and 1050 mg will be examined for safety, tolerability, PK, and pharmacodynamics of AMG 404 in subjects with advanced solid tumors. Rules for dose determination, and dose expansion are derived using a modified Toxicity

Probability Interval (mTPI) model (Ji et al. 2010) with a target toxicity probability interval (TPI) of 0.20 to 0.33 with a TPI $>$ 0.33 defined as excessive toxicity.

- Subjects will not be dosed at a level above the dose level indicated by the mTPI model. In particular, subjects will not be dosed at the current dose level or higher when the mTPI model indicates stopping enrollment at the current dose level and patients will not be dosed at an escalated dose level when the mTPI indicates staying at the current dose level.
- After reviewing a broad range of safety information including vital signs, laboratory values and detailed adverse events profiles, the team may choose to dose subjects below the dose level indicated by the mTPI model. For example, the team may choose to stop enrollment at the current dose level even if the mTPI model indicates staying at the current dose level.

The Dose Level Review Team (DLRT) will review data, monitor safety, and make recommendations on dose modifications based on all subjects that have been enrolled. A Dose Level Review Meeting will be conducted after Cohorts 1, 2 and 4 and may convene ad hoc to review safety data if deemed necessary.

Three dose levels are planned to be tested:

- Cohort 1: 240 mg every 4 weeks (N = 2-4)
- Cohorts 2 and 3: 480 mg every 4 weeks (Cohort 2: N = 6-9; Cohort 3: N = 20)
- Cohort 4: 1050 mg every 4 weeks (N = 20)

Dose escalation will begin with a run-in dose level of 240 mg (Cohort 1). If no DLTs are observed in Cohort 1, dose escalation will continue to the next planned dose level in Cohort 2. If DLTs are observed in Cohort 1, subsequent dosing will be determined by Amgen after consulting with the Dose Level Review Team (DLRT) and constrained by the mTPI model.

The table below shows rules for dose determination and dose expansion per the mTPI model.

Table 2-1. Guideline for Dose Level Decisions

No. of Subjects	Number of DLT observed at current dose		
	ESCALATE[a]	STAY AT CURRENT DOSE	STOP ENROLLMENT AT CURRENT DOSE
3	N/A	≤ 1	≥ 2
4	N/A	≤ 1	≥ 2
5	N/A	≤ 2	≥ 3
6	0	1 – 2	≥ 3
7	≤ 1	2 – 3	≥ 4
8	≤ 1	2 – 3	≥ 4
9	≤ 1	Maximum sample size reached	Maximum sample size reached

[a] For Cohort 4 (1050 mg), if the rules for dose escalation are met, enrollment may be stopped as there is sufficient evidence that 1050 mg dose is safe and tolerable; and this is the highest planned dose level being investigated on study.

Cohort 3

Upon completion of Cohort 2 of the study and depending on data obtained, dose expansion may proceed with the planned dose of 480 mg in Cohort 3 (N = 20) outside of China.

Cohorts 5-9

Upon completion of the first 6-9 subjects in Cohort 4 of the study and depending on data obtained, dose expansion may proceed with the RP2D in Cohort 5 with a safety lead-in (from China or NMPA certified sites in Taiwan and/or Hong Kong only) and Cohorts 6-9 (from all countries participating on the study, excluding China). The RP2D will be determined following review of available data obtained in Cohorts 1 through 4 including safety, tolerability, PK and PD data. [redacted].

Cohort 5 **was** a China**/Taiwan/Hong Kong-**specific expansion cohort with a safety lead-in at one dose below the RP2D followed by evaluation at RP2D, as appropriate. Up to 12 subjects **would** be enrolled in China, and/or in Taiwan, and/or Hong Kong (if Taiwan or Hong Kong, only NMPA certified sites will participate). [redacted]

Intrasubject dose escalation for Cohorts 1-9

Intra-Subject dose escalations are allowed on this study for subjects enrolled, where applicable. Subjects enrolled to Cohort 1 who complete the DLT period may proceed to 480 mg once Cohort 2 has been deemed safe by the DLRT; subjects receiving 480 mg

(in Cohorts 1-3) who complete the DLT period may proceed to the RP2D once determined if a dose higher than 480 mg is selected as the RP2D. Subjects enrolled to the safety lead-in dose in Cohort 5, may escalate to the RP2D dose level once the RP2D is determined safe following the China/Taiwan/Hong Kong specific DLRT recommendation. [redacted].

All intra-subject dose escalations may occur after consultation with the sponsor if:

- No DLT has been reported for this subject during or after completion of the DLT period

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

[redacted]

[redacted]

Number of Subjects

Cohort 1: Up to 4 evaluable subjects may be enrolled to this cohort.

Cohort 2: Up to 9 evaluable subjects may be enrolled to this cohort.

Cohort 3: An additional 20 evaluable subjects will be enrolled in the dose expansion part of the study outside of China.

Cohort 4: Up to 20 evaluable subjects may be enrolled to this cohort.

Cohort 5: Approximately 12 evaluable subjects will be enrolled from China, or from National Medical Products Administration (NMPA) certified sites in Taiwan and/or Hong Kong [redacted]

Cohort 6: Approximately 20 evaluable subjects will be enrolled in the dose expansion at the RP2D outside of China.

Cohort 7: Up to 40 evaluable subjects

Cohort 8: Up to 40 evaluable subjects

Cohort 9: Up to 40 evaluable subjects

[redacted]

Summary of Subject Eligibility Criteria

Adult subjects (≥ 18 years old) with histologically or cytologically proven metastatic or locally advanced solid tumors who are checkpoint inhibitor naïve. Subjects enrolled to

Cohort 9 may not have received prior systemic treatment for their metastatic or recurrent disease (prior neoadjuvant, adjuvant, and/or chemotherapy given concurrently with definitive radiation is allowed).

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, [redacted], please refer to Section 7.1 and Section 7.2.

Treatments

In Cohorts 1-9, AMG 404 will be administered intravenously (IV) over approximately 30 minutes, every 4 weeks in subjects with advanced solid tumors.

Three dose levels are planned to be tested:

- Cohort 1: 240 mg every 4 weeks (N = 2-4)
- Cohorts 2 and 3: 480 mg every 4 weeks (Cohort 2: N = 6-9; Cohort 3: N = 20)
- Cohort 4: 1050 mg every 4 weeks (N = 20)

Upon completing Cohort 2 of the study and depending on data obtained, the dose expansion may proceed with the planned dose of 480 mg in Cohort 3 (N = 20) outside of China.

After the first 6-9 subjects have completed the DLT evaluation period in Cohort 4 of the study and depending on data obtained, the dose expansion may proceed with the RP2D in Cohorts 5-9, [redacted]

[redacted]

Procedures

After written informed consent has been obtained, all screening tests and procedures will be performed within 28 days of administration of the first dose (cycle 1, day 1) of AMG 404, unless otherwise noted. Subjects will be seen in clinic where critical clinical safety and study evaluations will be performed including physical examination, vital signs, clinical laboratory tests, electrocardiograms (ECGs), PK, and [redacted] sample collections.

For a full list of study procedures, including the timing of each procedure, please refer to General Assessments (Section 10.2) and the Schedule of Activities (for Cohorts 1-9,

refer to Table 3-1 [redacted]

Statistical Considerations

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

The DLRT will review data, monitor safety, and make recommendations on dose modifications based on all subjects that have been enrolled. Rules for dose determination and dose expansion are derived using a modified Toxicity Probability Interval (mTPI) model.

Descriptive statistics will be provided for selected demographics, safety, PK, efficacy [redacted] by **cohort, or** time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages.

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

The proportion of subjects with an objective tumor response (partial and complete response) and disease control rate (DCR) (partial or complete control) with corresponding exact 80% CI will be calculated and tabulated. Similarly, the proportion of subjects and 80% CI will be tabulated for 1-year duration of overall response, 1-year PFS, 1-year duration of stable disease **and 1-year OS**. Kaplan-Meier curves will be presented for duration of overall response, PFS, **OS,** and duration of stable disease with estimates for rate and 80% CI at selected weeks if data allows.

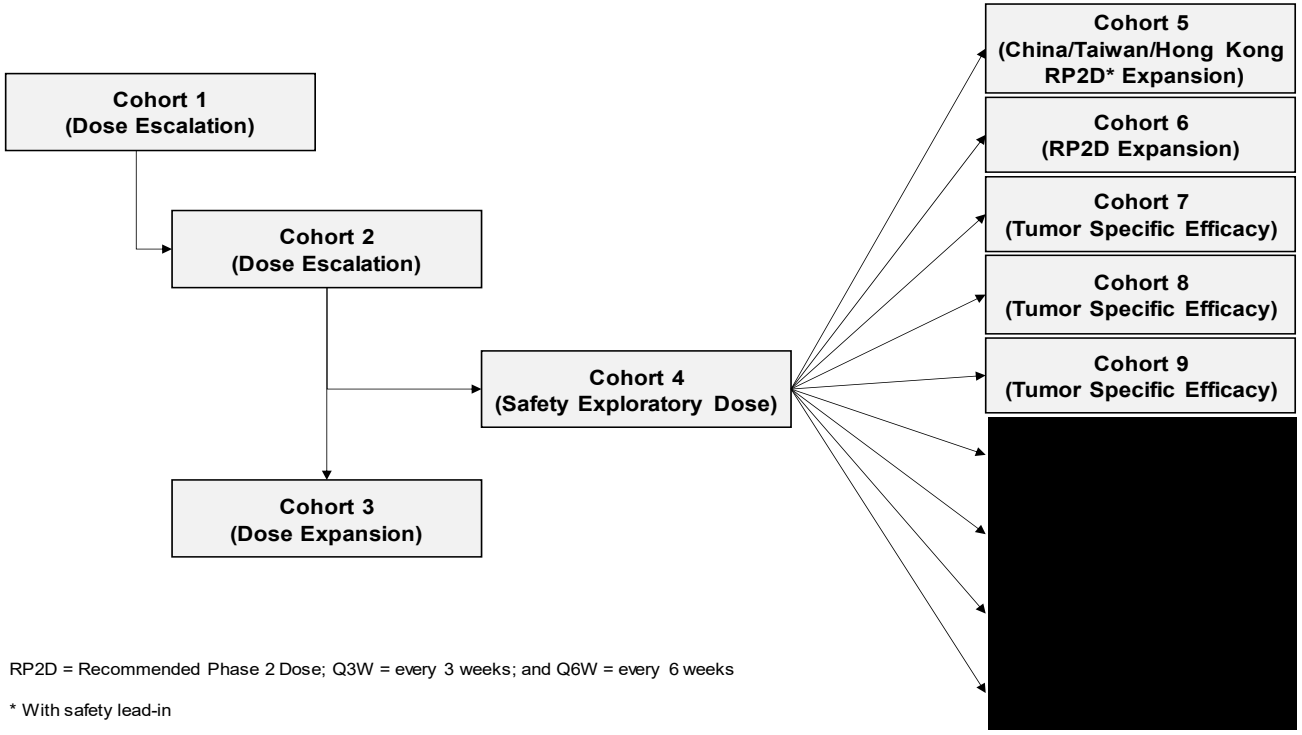
For a full description of statistical analysis methods, please refer to Section 11.

Sponsor Name: Amgen Inc.

3. Study Schema and Schedule of Activities

3.1 Study Schema

Figure 3-1. Study Schema

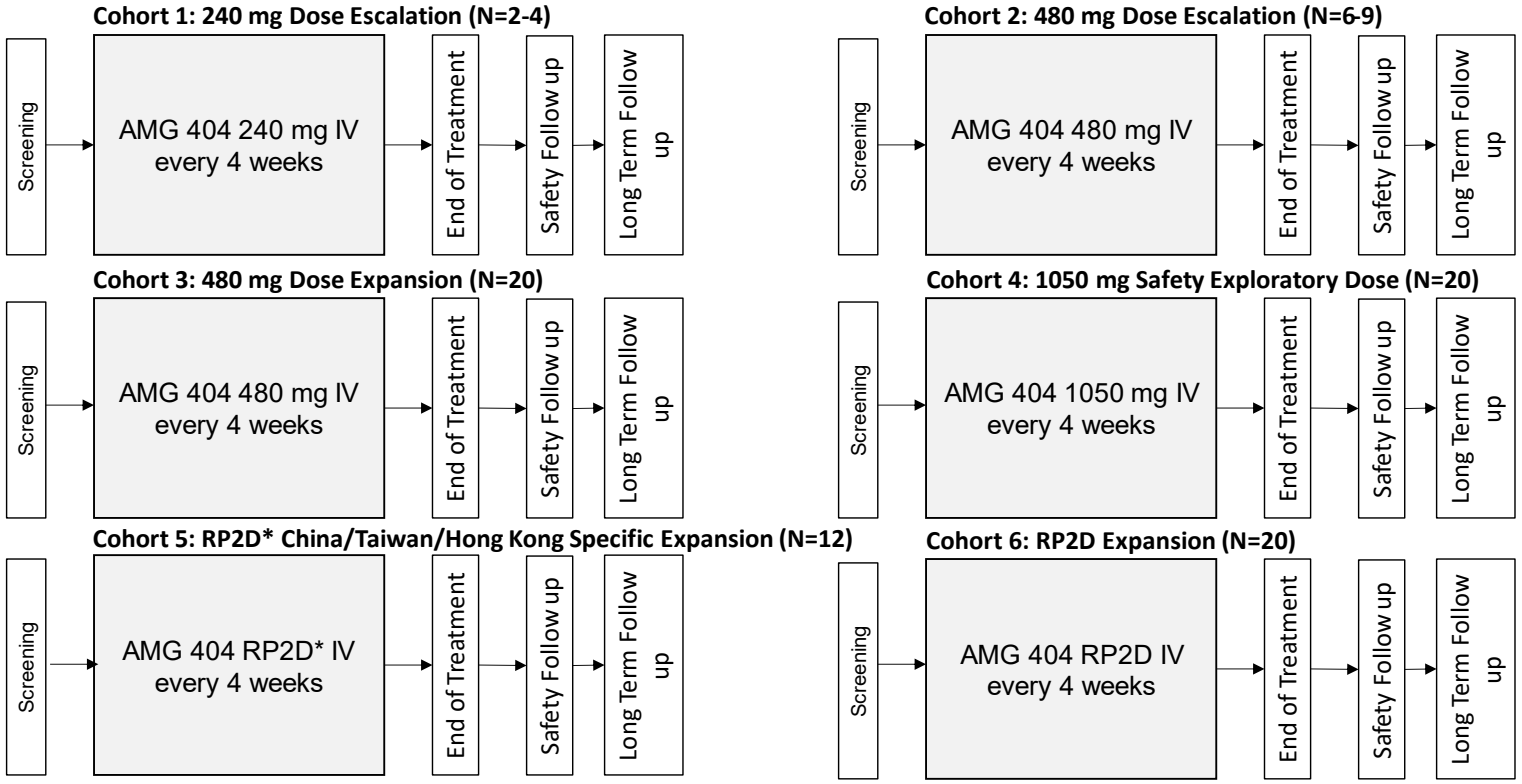


RP2D = Recommended Phase 2 Dose; Q3W = every 3 weeks; and Q6W = every 6 weeks

* With safety lead-in

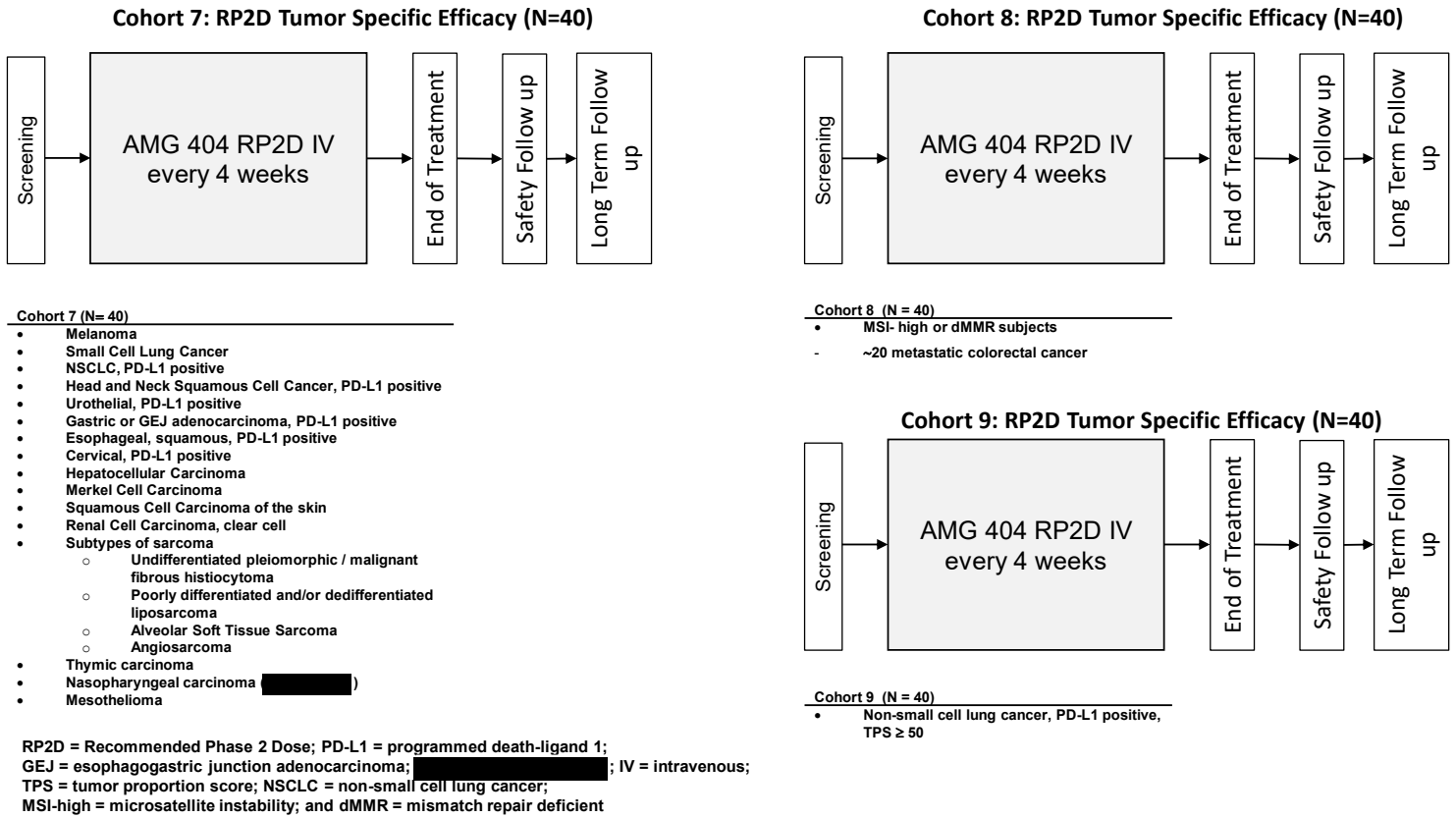
Refer to the schematics for each cohort below and Section 6.1 for further details

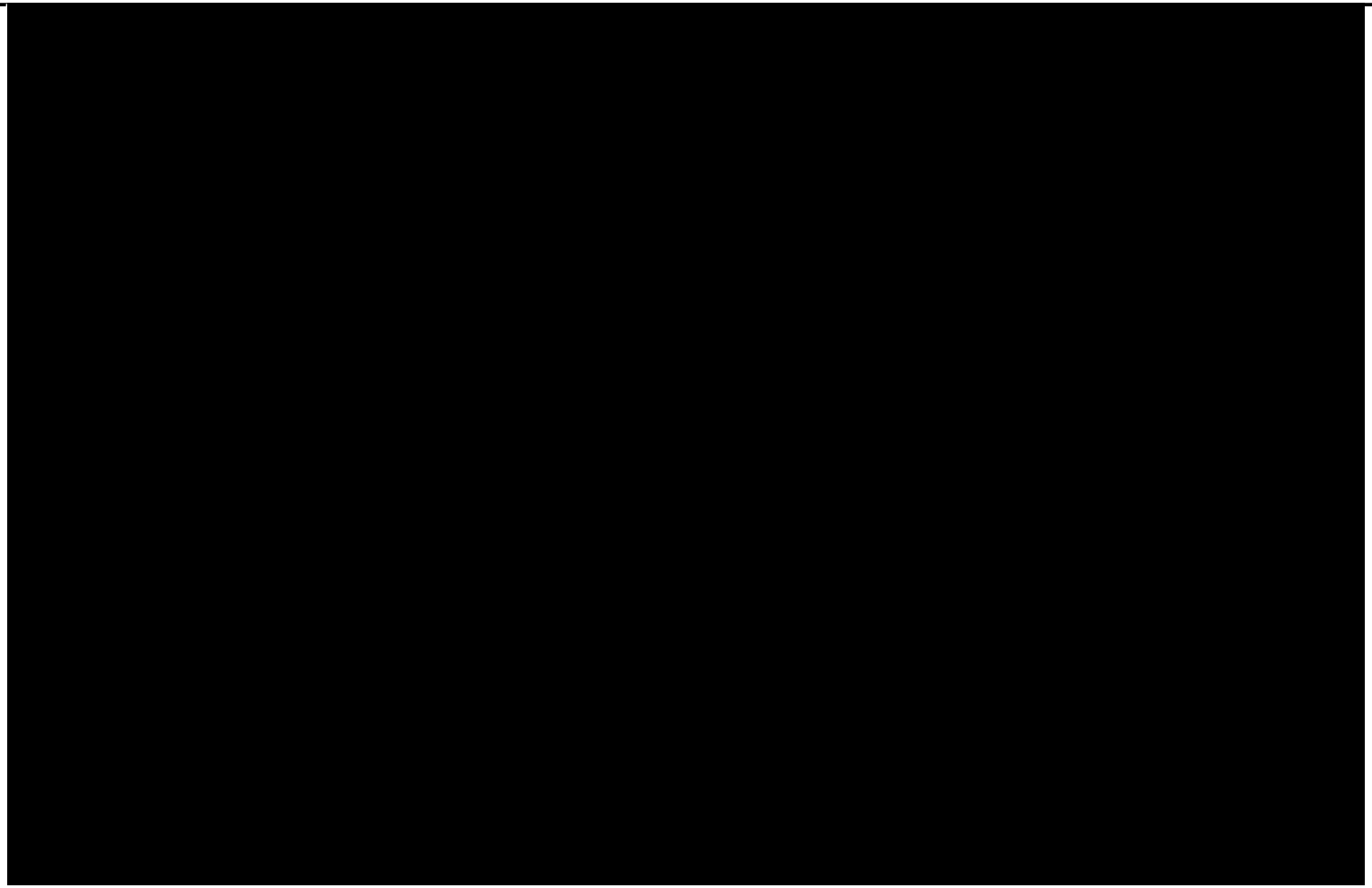
Figure 3-2. Study Schema



RP2D = Recommended Phase 2 Dose; and IV = intravenous
* With safety lead-in

Figure 3-3. Study Schema





3.2 Schedule of Activities

Table 3-1. Schedule of Activities for Cohorts 1-9

CYCLES	Screening (up to 28 days before Day 1)	Treatment Period																				Follow-up		
		1*								2*								3* and beyond		Extended Treatment				
DAYS		1*				2	4	8 (±1d)	15 (±1d)	1*				2	4	8 (±1d)	15 (±1d)	1*		1*		EOT[12]	Safety F/U[10, 12]	LTFU[10]
Hours (relative to end of infusion)		Pre dose	0 EOI	2	4	24	72	168	336	Pre dose	0 EOI	2	4	24	72	168	336	Pre dose	0 EOI	Pre dose	0 EOI			
GENERAL AND SAFETY ASSESSMENTS																								
Informed consent	X																			**X**				
Inclusion and exclusion criteria	X																							
Demographics	X																							
Physical examination, ECOG PS, wt, (Ht at screening only)	X	X						X	X	X								X		**X**		X	X	
Medical history	X																							
ECG triplicate measurement[1]	X	X[1]	X[1]		X[1]						X[1]								X[1]		**X**[1]			
Vital signs	X	X	X	X	X			X	X	X	X	X	X					X	X	**X**	**X**	X	X	
Adverse events review			◄																		►			
Serious Adverse **E**vents[17]	X	◄																			►			
Concomitant medication review	X	◄																			►			
LABORATORY ASSESSMENTS																								
Pregnancy test (females of childbearing potential only)[2]	X	X								X								X		**X**		X	X	
Coagulation	X																							
Hematology	X	X						X	X	X								X		**X**		X	X	
Chemistry[3]	X	X						X	X	X								X		**X**		X	X	
HIV, Hepatitis B and C screening	X																							
Urinalysis	X	X								X								X		**X**		X	X	
ACTH, ANA, ANCA[4]	X	X[4]																X[4]		**X**[4]		X[4]	X[4]	

Footnotes defined on next page of this table

Table 3-1. Schedule of Activities for Cohorts 1-9

CYCLES	Screening (up to 28 days before Day 1)	Treatment Period																				Follow-up		
		1*								2*								3* and beyond		Extended Treatment				
DAYS		1*				2	4	8 (±1d)	15 (±1d)	1*				2	4	8	15	1*		1*		EOT[12]	Safety F/U[10, 12]	LTFU[10]
Hours (relative to end of infusion)		Pre dose	0 EOI	2	4	24	72	168	336	Pre dose	0 EOI	2	4	24	72	168	336	Pre dose	0 EOI	Pre dose	0 EOI			
RADIOLOGICAL ASSESSMENTS																								
Tumor Evaluation/staging (CT, MRI, as appropriate)[5]	X																	X[5]		**X[5]**		X		
[redacted]																								
Brain MRI or CT with contrast[5]	X																	X[5]		**X[5]**				
PHARMACOKINETIC ASSESSMENTS[6]																								
Cohorts 1–6 (all subjects), Cohorts 7–9 (at least 10 subjects of each cohort)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	
Cohorts 7–9 (remaining subjects)		X	X							X	X							X	X			X	X	
RESEARCH LABS, ALL SITES																								
ADA/Immunogenicity		X							X	X							X	X[9]				X	X	
Whole Blood for Cytometry[13]	X	X			X	X		X	X	X								X[8]						
[redacted]																								
LTFU																								
Phone Call																								X

Footnotes defined on next page of this table

* A Cycle is defined as 28 (±3) days; Day 1 assessments must be done within 48 hours of AMG 404 infusion; screening assessments if done within 48 hours do not have to be repeated on day 1 of treatment; AMG 404 will be infused on Day 1 after all safety assessments have been completed.

CT = computed tomography; [redacted] ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; **EOT = end of treatment**; HIV = human immunodeficiency virus; **LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; SFU = safety follow-up.**

[1] A set of triplicate ECGs must be performed at screening; all ECGs will be triplicates with each tracing approximately 30 seconds apart and run consecutively. ECGs will only be collected for subjects enrolled to Cohorts 1, 2 and 4 at the following time points: Screening, C1D1 predose and end of infusion, C1 D1 (4 hours post dose), C2D1 end of infusion, C3D1 end of infusion, C4D1 end of infusion, and C5D1 end of infusion. Beginning with Cycle 6 and beyond for subjects enrolled to Cohorts 1, 2 and 4 will have ECGs performed if clinically indicated. Subjects enrolled to Cohort 3 and Cohorts 5-9 will have an ECG performed at screening and then as clinically indicated.

[2] Pregnancy testing is required for all female subjects of childbearing potential. Serum pregnancy test at screening and 48 hours prior first dose of AMG 404. Beginning with cycle 2 and beyond, a urine or serum pregnancy test is required within 48 hours prior to AMG 404 infusion.

[3] Chemistry to include: Albumin, Alkaline Phosphatase, ALT, AST, BUN/Total urea, **Bicarbonate or CO2,** Calcium, **Calcium Corrected,** Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total protein, TSH, Free T4

[4] ACTH to be done at screening, prior to C1D1, and then every 8 weeks (prior to cycles 1, 3, etc). ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.

[5] [redacted] tumor evaluation scans every 8 (± 1) weeks, same modality should be used throughout study. MRI or CT of brain required for all subjects during screening and required on study only if subject has history of CNS disease; otherwise as clinically indicated. If a subject discontinues treatment for reasons other than progression, tumor assessments should continue in follow up every 8 (±1) weeks until progression or start of a new treatment regimen. **Subjects with extended treatment will undergo tumor evaluation scans every 12 (± 2) weeks, and MRI or CT of brain as clinically indicated.**

[6] PK blood samples should be collected at the exact nominal time point as noted above (see hour postdose column). If unable to collect a blood sample at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations.

[redacted]

[9] Beginning with cycle 3, ADA/Immunogenicity sample collected every cycle, predose (ie, cycle 3, cycle 4, cycle 5, etc).

[10] Safety follow-up visit is to take place 30 (+ 3) days and 140 days (±7 days) after last dose. Long-term follow-up phone call at 6 months (±1 week) after last dose to collect information on survival, start of new therapies, and disease status.

[redacted]

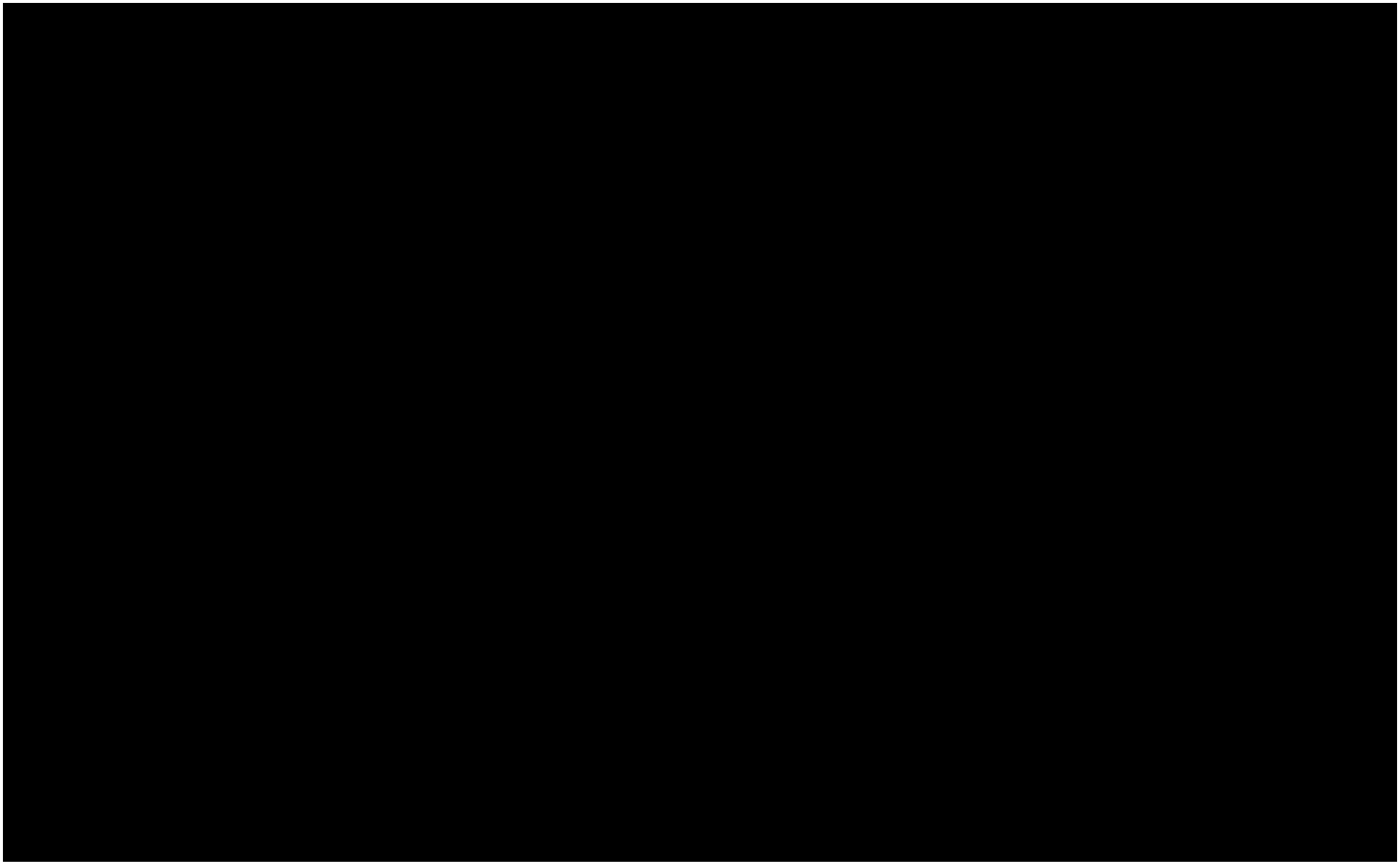
[12] The EOT and SFU may be combined if the visit occurs 30 (+ 3) days after the last dose of AMG 404. **In addition, for subjects that continue treatment of AMG 404 in the extended treatment period only, assessments for ADA/immunogenicity and PK will not be collected at EOT and SFU visits.**

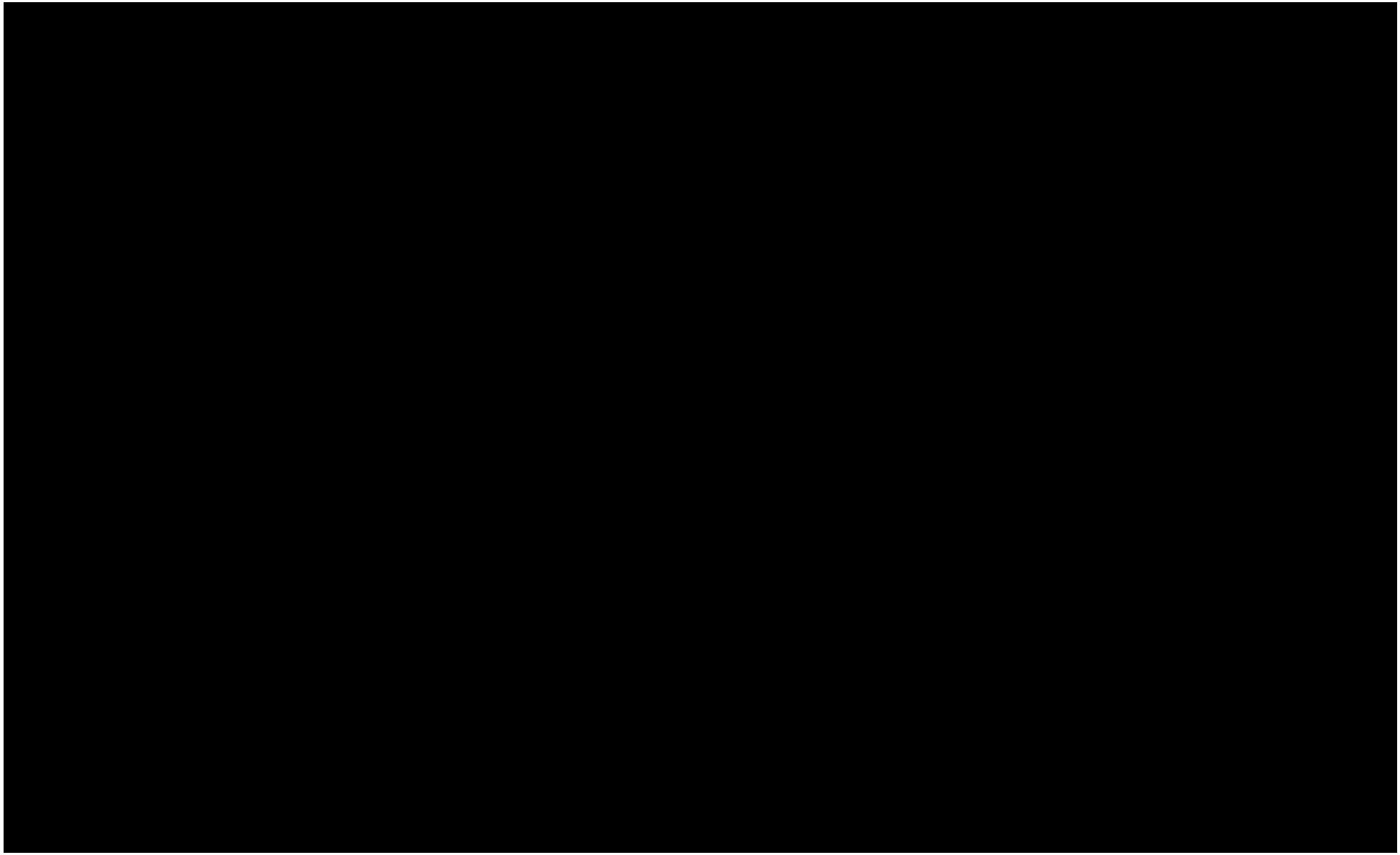
[13] Whole blood cytometry collections are required for Cohorts 1-6 only for receptor occupancy immunophenotyping. Last sample is collected cycle 3 predose (not required cycle 4 and beyond).

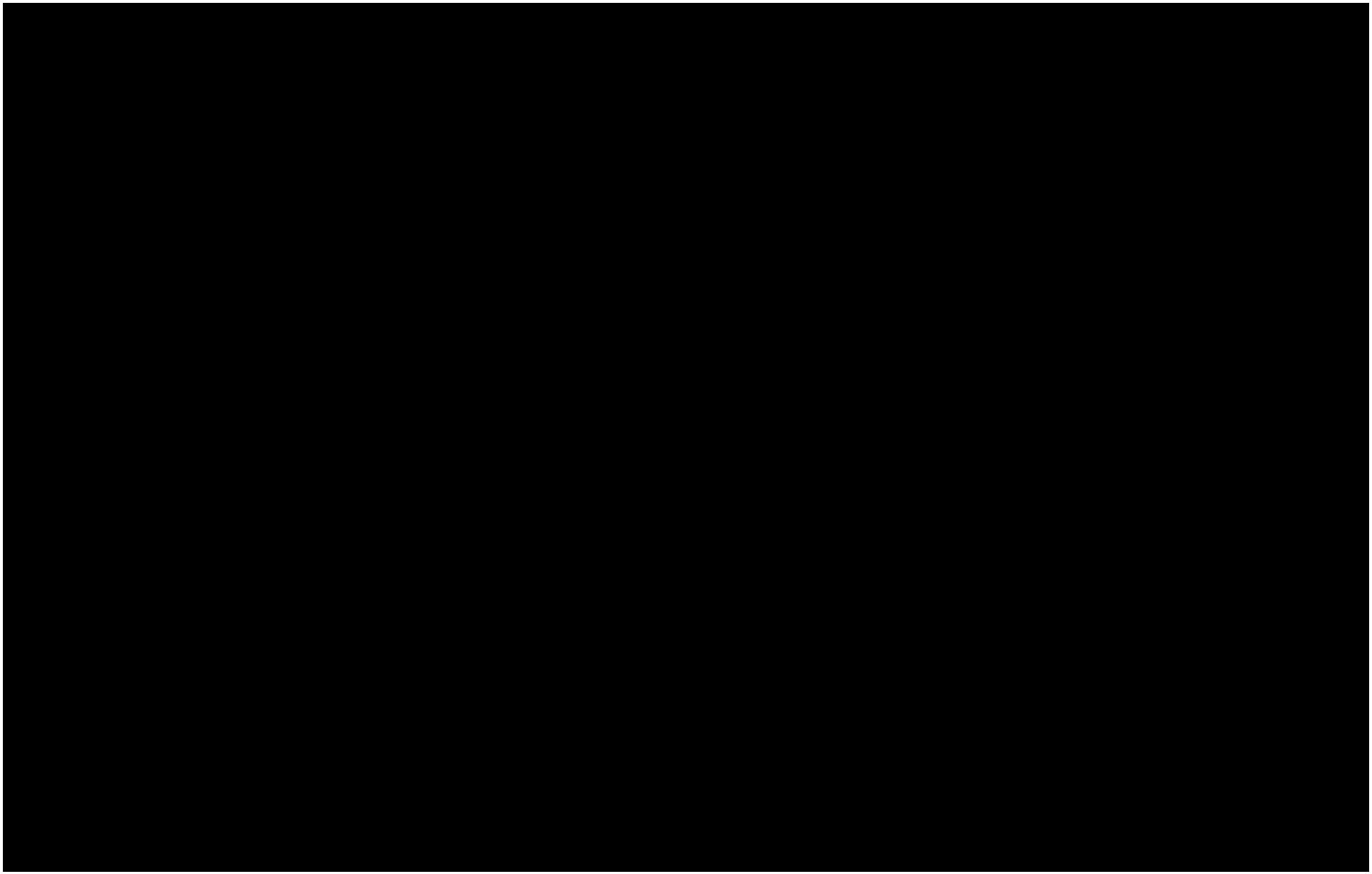
[14] Whole blood immunophenotyping collections are required for Cohorts 7-9 only for analysis of lymphocyte activation and exhaustion. Last sample is collected cycle 3 predose (not required cycle 4 and beyond)

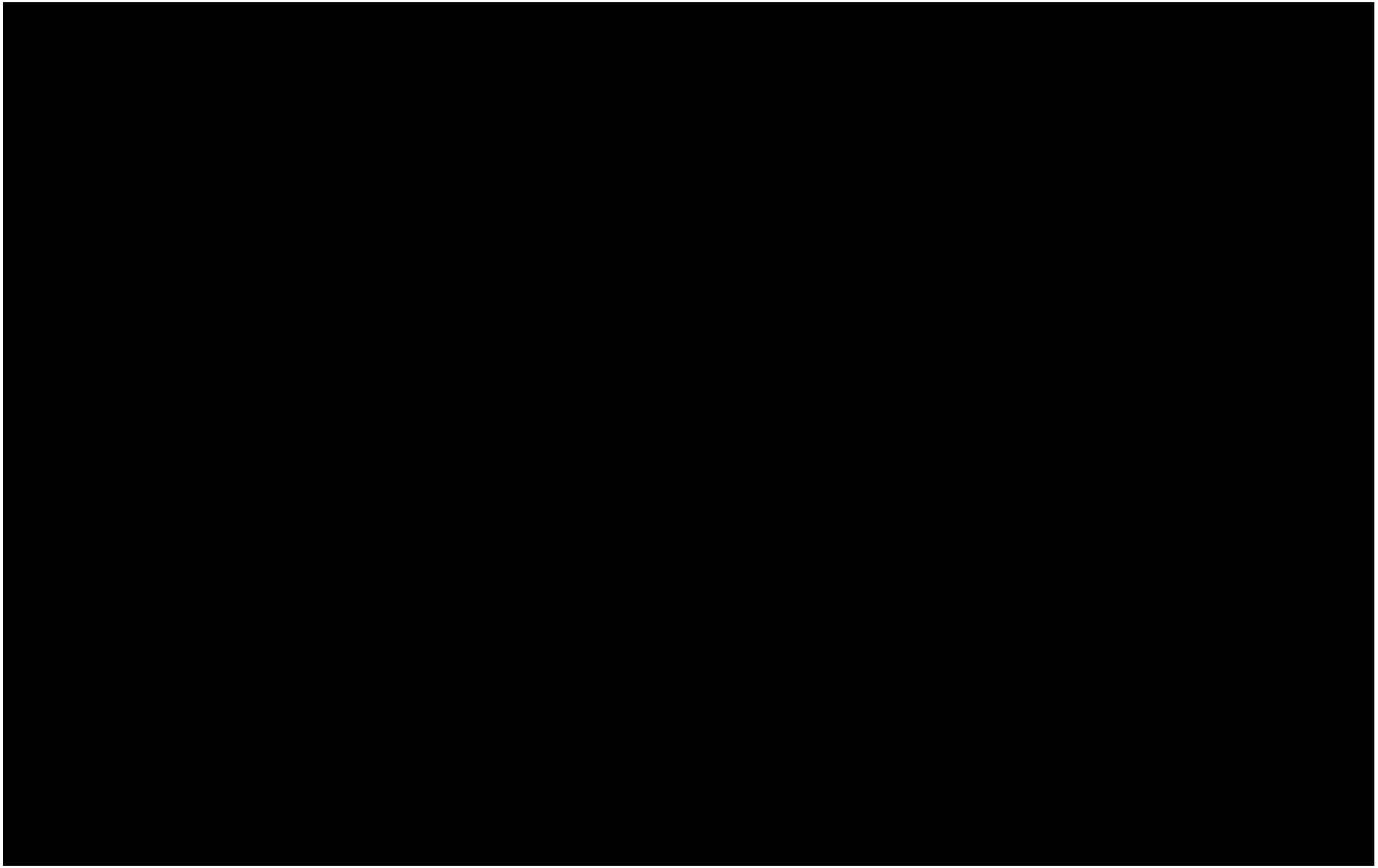
[redacted]

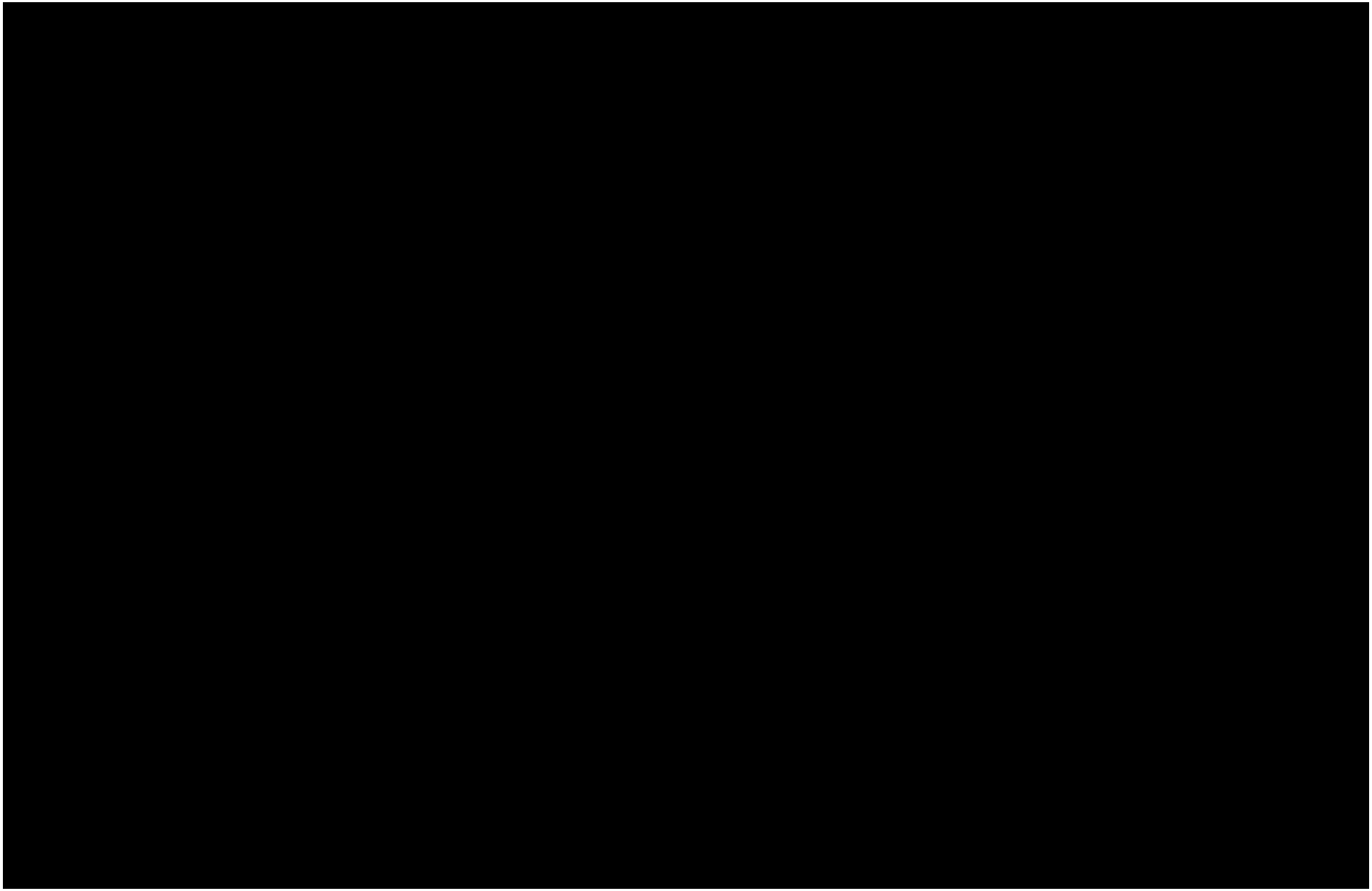
During the long-term follow-up phase serious adverse events suspected to be related to investigational products that the investigator becomes aware of will be reported to Amgen. After end of study, serious adverse events suspected to be related to investigational products will be reported to Amgen. Please refer to Section 10.2.3.1.1.3 for additional details.

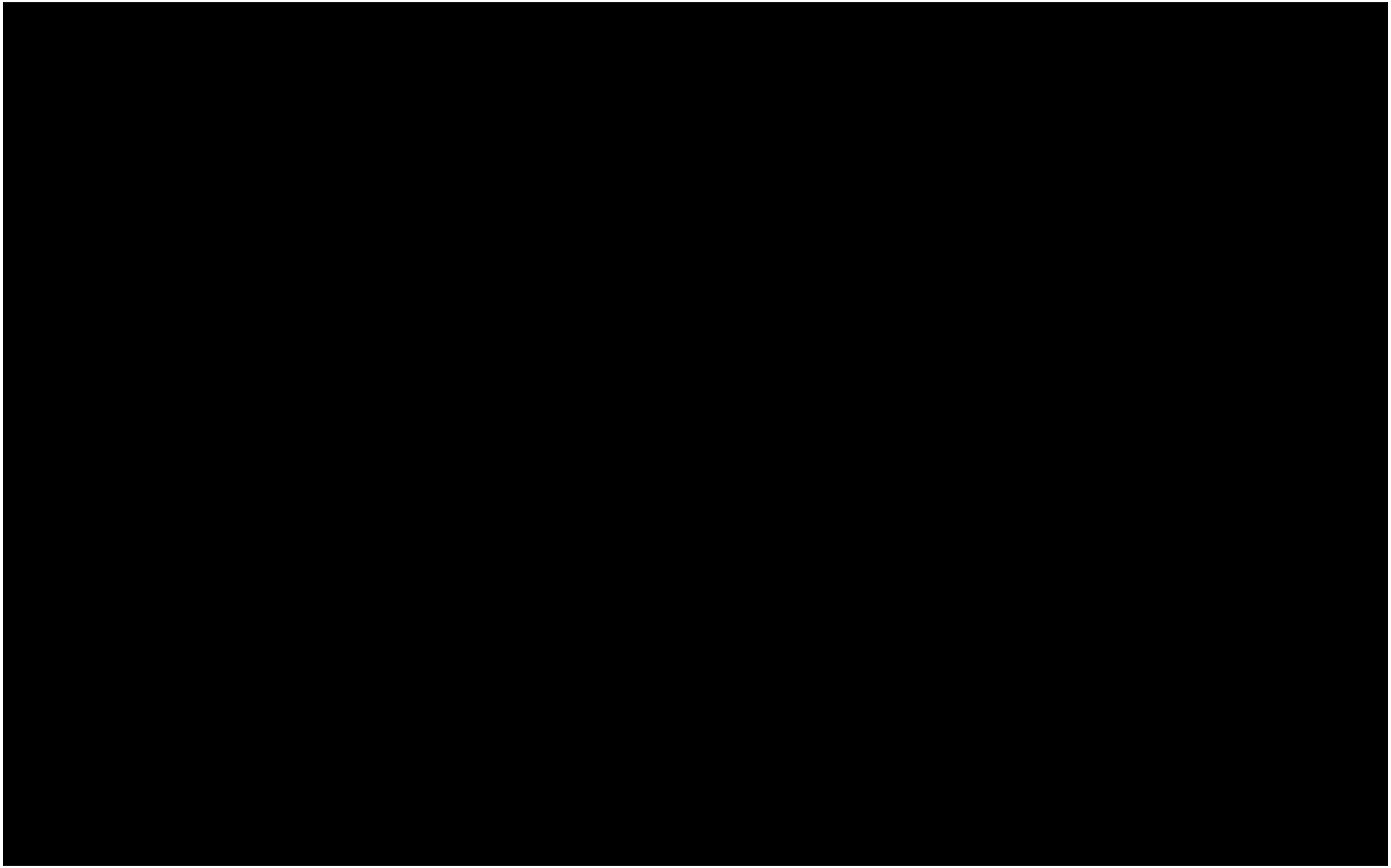












4. Background and Rationale

4.1 Disease and Target Background

Anti-tumor surveillance by the immune system is a well-known mechanism to prevent growth and spread of malignancies. This natural defense mechanism is, however, susceptible to fatigue. T cells can lose their efficacy through increased expression of the programmed cell death-1 (PD-1) proteins and their ligands, PD-L1. (Riley et al, 2009).

The programmed cell death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control (Pedoeem et al, 2014). The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).

Enhancement of anti-tumor immunity through inhibition of PD-1/PD-L1 has been effective in treatment of many malignancies (Pembrolizumab US Prescribing Information, Nivolumab US Prescribing Information and Cemiplimab US Prescribing Information). For example, use of PD-1/PD-L1 monoclonal antibodies have resulted in objective tumor response and/or improved survival in lung cancer, melanoma, urothelial carcinoma, head and neck squamous cell carcinoma, and cutaneous squamous cell carcinoma (Gong et al, 2018).

While objective responses have been achieved in many patients, some do not benefit from anti-PD-1 monotherapy. Optimal therapy will likely require combining anti-PD-1 monoclonal antibody treatment with conventional therapies and novel targeted or immunotherapy approaches.

The use of combinations of chemotherapy, targeted therapy, and other checkpoint inhibitors and immune modulating agents along with PD-L1 inhibitors is being investigated in multiple disease states and has been shown to improve efficacy over some of the former standard therapies (for example, in non-small cell lung cancer in combination with chemotherapy or in combination with chemotherapy and antiangiogenic therapy [Socinski et al, 2018], and in melanoma in combination with CTLA-4 inhibitors [Wolchok et al, 2017]).

4.1.1 PD-1/PD-L1 Inhibitors and Treatment of NSCLC

Programmed cell death-1 checkpoint blockade has transformed the treatment of NSCLC. Programmed cell death-1, and then PD-L1 inhibitors were first approved for NSCLC in the second line or later setting based on studies showing significant anti-tumor activity and improved overall survival in both squamous and non-squamous NSCLC when compared to docetaxel alone. Nivolumab, pembrolizumab, and atezolizumab are approved by the United States Food and Drug Administration (US FDA) for treatment of second line or later advanced or metastatic NSCLC (Doroshow et al, 2019).

In the front-line setting, clinical trials with PD-1/ PD-L1 inhibitors have demonstrated improved overall survival when given as monotherapy in PD-L1 expressing tumors and in combination with chemotherapy. Pembrolizumab is US FDA approved for first line monotherapy in advanced NSCLC expressing PD-L1 with tumor proportion score (TPS) $\geq$ 1% (Keytruda USPI). Cemiplimab is approved for the first-line treatment of NSCLC with high PD-L1 TPS $\geq$ 50% (Libtayo USPI). Atezolizumab is also approved for first-line treatment of tumors with high PD-L1 expression (Tecentriq USPI). The addition of PD-1/PD-L1 inhibitors to first line chemotherapy demonstrated improvement in overall survival in metastatic NSCLC regardless of PD-L1 expression. (Chiang et al, 2020). The Keynote-189 study compared pembrolizumab, platinum-based drug, and pemetrexed to placebo, carboplatin, and pemetrexed in subjects with non-squamous NSCLC and reported a 12 month overall survival of 69.2% versus 49.4%
(HR = 0.49; 95% CI: 0.38 to 0.64; P < 0.001), and led to the FDA approval of pembrolizumab, platinum-based drug, and pemetrexed for first line treatment of metastatic nonsquamous NSCLC regardless of PD-L1 expression (Gandhi et al, 2018).

4.2 Amgen Investigational Product Background: AMG 404

4.2.1 Nonclinical Pharmacology

AMG 404 is a fully human antibody that binds human and cynomolgus monkey PD-1 with high affinity and blocks the ability of these receptors to interact with human ligands, PD-L1 and PD-L2. The ligand blocking activity of AMG 404 was evaluated in three different assays using three different readouts and both cell-expressed, as well as recombinant, soluble ligands. In each assay, AMG 404 demonstrated the expected dose-dependent activity, indicating it is a potent inhibitor of human and cynomolgus monkey PD-1 binding.

AMG 404 blocks the interaction between cynomolgus monkey PD-1 and human PD-L1 with a similar IC_{50} as human PD-1 and human PD-L1, suggesting that cynomolgus monkey is an appropriate species for nonclinical safety evaluation.

AMG 404 is an IgG1 antibody; however, the Fc region has been modified to eliminate undesired interactions with Fc gamma receptors. The absence of Fc-binding to Fc gamma receptors was demonstrated in a functional assay where the ability of AMG 404 to induce ADCC activity was compared to a positive control anti-CD38 antibody and negative control antibodies. In this assay, AMG 404 activity was comparable to the negative control antibodies and was much less than the positive control. These results demonstrate that the Fc region of AMG 404 does not interact with Fc gamma receptors.

4.2.2 Toxicology

The potential for AMG 404 to cause acute release of cytokines from human peripheral blood leukocytes (PBL) in the presence of human endothelial cells (HUVECs) was evaluated in vitro. Human PBL were cultured in autologous Platelet Poor Plasma (PPP) in the presence of HUVECs with AMG 404 (0.0112 – 35 µg/mL) for 24 hours, and supernatants from the cultures were subsequently assessed for the presence of cytokines (IFNγ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 p70, and TNFα). Under the

conditions tested in this assay, AMG 404 did not induce cytokine release above background levels.

AMG 404 was evaluated in a 28-day GLP toxicology study in cynomolgus monkeys. Doses of 0, 10 or 100 mg/kg were administered by slow IV bolus, and doses of 0 or 100 mg/kg were administered SC (3 animals/sex/group). Animals were dosed once weekly (4 total doses). There were no AMG 404-related clinical signs or effects on body weight, food consumption, respiratory rate, body temperature, organ weights, or urinalysis parameters and no AMG 404-related ocular, electrocardiographic, neurologic, or macroscopic findings. AMG 404-related clinical pathology changes were limited to mild decreases in lymphocytes for females at all dose levels on Day 2 that were generally similar to control and/or baseline values on Day 9 and throughout the remainder of the study, and mildly increased C-reactive protein in some animals. AMG 404-related microscopic findings included an increased incidence and/or severity of mononuclear cell infiltration in the brain (minimal to mild) and/or spinal cord (minimal) of animals given ≥ 10 mg/kg IV or 100 mg/kg SC and at the administration site (minimal to mild) of males given 100 mg/kg SC. The increased incidence and/or severity of mononuclear cell infiltration in the brain and/or spinal cord observed in this study may represent an exacerbation of this background finding in cynomolgus monkeys, while the mononuclear cell infiltration at the administration site was considered an expected reaction to the administration of an exogenous protein. In conclusion, administration of AMG 404 by once weekly IV bolus or SC injection was well tolerated in cynomolgus monkeys at levels of 10 mg/kg IV and 100 mg/KG IV and SC.

4.2.3 Nonclinical Pharmacokinetics

The PK of AMG 404 was characterized after single intravenous (IV) bolus injection at 0.5 and 5 mg/kg and single subcutaneous (SC) injection at 5 mg/kg to male cynomolgus monkeys. Serum concentrations of AMG 404 declined in a biphasic manner for the first 168 hours post dose followed by a more rapid decrease, most likely because of the formation of anti-AMG 404 antibodies (ADA) which were observed in all animals at 336 hours post dose.

The toxicokinetics (TK) of AMG 404 were characterized in a Good Laboratory Practice (GLP) study after weekly IV administration of 10 or 100 mg/kg or SC administration of 100 mg/kg for four consecutive weeks. Following repeat dose administration, AMG 404 exposure increased approximately dose-proportionally from 10 to 100 mg/kg as

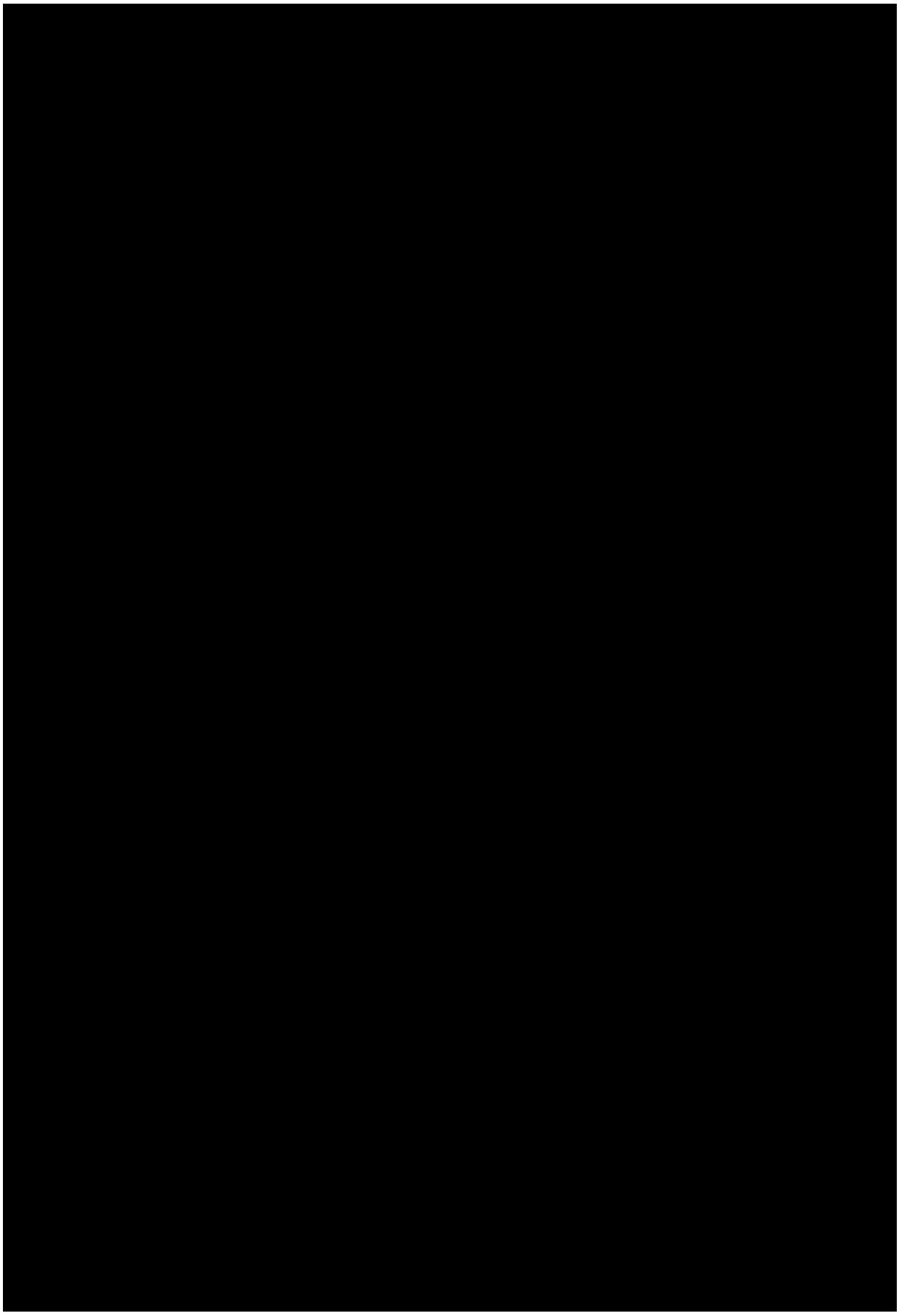
measured by C_{max} and AUC over 6 days. AMG 404 exposures were similar between male and female animals.

4.2.4 Rationale for Development AMG 404

Blockade of the PD-1/PD-L1 T-cell checkpoint pathway is an effective and generally well tolerated approach to stimulating immune response to tumor cells. While objective responses have been achieved in many patients, some do not benefit from PD-1 monotherapy. Optimal therapy will likely require combining anti-PD-1 monoclonal antibody treatment with conventional therapies and novel targeted or immunotherapy approaches. Amgen is developing a large oncology portfolio and to maximize this portfolio for patient benefit, Amgen is developing AMG 404. Access to AMG 404 allows Amgen to develop a deeper understanding of target engagement and pharmacodynamic profile in combination with our portfolio and facilitates more rapid dosing and dose frequency adaptations while studying across multiple malignancies (solid tumors and hematologic malignancies).

This study will evaluate AMG 404 as a monotherapy [redacted] to determine safety and tolerability. [redacted]

[redacted]



[redacted]

4.5 Benefit/Risk Assessment

AMG 404

This is a first-in-human study with AMG 404. Based on nonclinical toxicity studies of AMG 404, clinical experience with AMG 404, and clinical experience with other anti-PD(L) -1 therapies, the overall benefit/risk profile favors clinical development of AMG 404 for patients with advanced solid tumors.

[redacted]

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.

The following benefit/risk assessment supports the conduct of this clinical trial. Refer to the AMG 404 Investigator's Brochure for further information.

4.5.1 Therapeutic Context

AMG 404

AMG 404 will be investigated in subjects with advanced solid tumors as monotherapy

[redacted]

4.5.2 Benefits

AMG 404

As AMG 404 is in early development and clinical experience is limited, key benefits are being investigated and will be described when the data become available.

[redacted]

4.5.3 Risks

AMG 404

AMG 404 is being evaluated as an ongoing monotherapy in the current study. Based on **the available** clinical **data** with AMG 404**, hypothyroidism, colitis, pneumonitis, and myasthenia gravis are identified risks** of AMG 404 (see Table 4-1).

Table 4-1. Key Safety Risks of AMG 404

Safety Risk	Description
Hypothyroidism	**Administration of AMG 404 has been associated with hypothyroidism or blood thyroid stimulating hormone increased. Signs and symptoms that may be associated with hypothyroidism include fatigue, increased sensitivity to cold, constipation, dry skin, weight gain, hoarseness, muscle weakness, myalgia, arthralgia, menstrual disturbance, alopecia, bradycardia, hypercholesterolemia, depression, impaired memory, and enlarged thyroid gland (goiter).** **Hypothyroidism or blood thyroid stimulating hormone increased reported events did not lead to AMG 404 discontinuation or AMG 404 treatment interruption. Subjects should be monitored for laboratory values of thyroid stimulating hormone and Free T4, and signs and symptoms of hypothyroidism during AMG 404 treatment. Subjects should continue to be monitored after discontinuation of AMG 404 due to the risk of late onset hypothyroidism. Requirements for monitoring and management of hypothyroidism are provided in the clinical study protocol.**
Colitis	**Administration of AMG 404 has been associated with colitis. Signs and symptoms that may be associated with colitis include diarrhea, abdominal pain, abdominal cramping, and blood or mucus in the stool.** **Colitis events have led to AMG 404 discontinuation. Subjects should be monitored for signs and symptoms of colitis during AMG 404 treatment. Subjects should continue to be monitored after discontinuation of AMG 404 due to the risk of late onset colitis. Requirements for monitoring and management of colitis are provided in the clinical study protocol(s).**
Pneumonitis	**Administration of AMG 404 has been associated with pneumonitis. Signs and symptoms that may be associated with pneumonitis include cough, shortness of breath, chest pain and fatigue. Pneumonitis events have led to discontinuation of AMG 404. Subjects should be monitored for signs and symptoms of pneumonitis during AMG 404 treatment. Subjects should continue to be monitored after discontinuation of AMG 404 due to the risk of late onset pneumonitis. Requirements for monitoring and management are provided in the clinical study protocol(s).**
Myasthenia Gravis	**Administration of AMG 404 has been associated with the serious myasthenia gravis in one subject in a combination study of AMG 404 and AMG 160 for prostate cancer.** **Signs and symptoms that may be associated with myasthenia gravis include diplopia, ptosis, muscle weakness and fatigability, difficulty with speech, swallowing, and/or breathing. Myasthenia gravis event led to permanent discontinuation of the study drugs. Subjects should be monitored for signs and symptoms of myasthenia gravis during AMG 404 treatment.**

Additional key safety information, which are based on the mechanism of action, the nonclinical safety pharmacology and toxicology studies for AMG 404, available data from the ongoing clinical study, and class effects of approved PD-1/PD-L1 checkpoint inhibitors, but for which a causal association with AMG 404 has not been established, are summarized below (see Table 4-2).

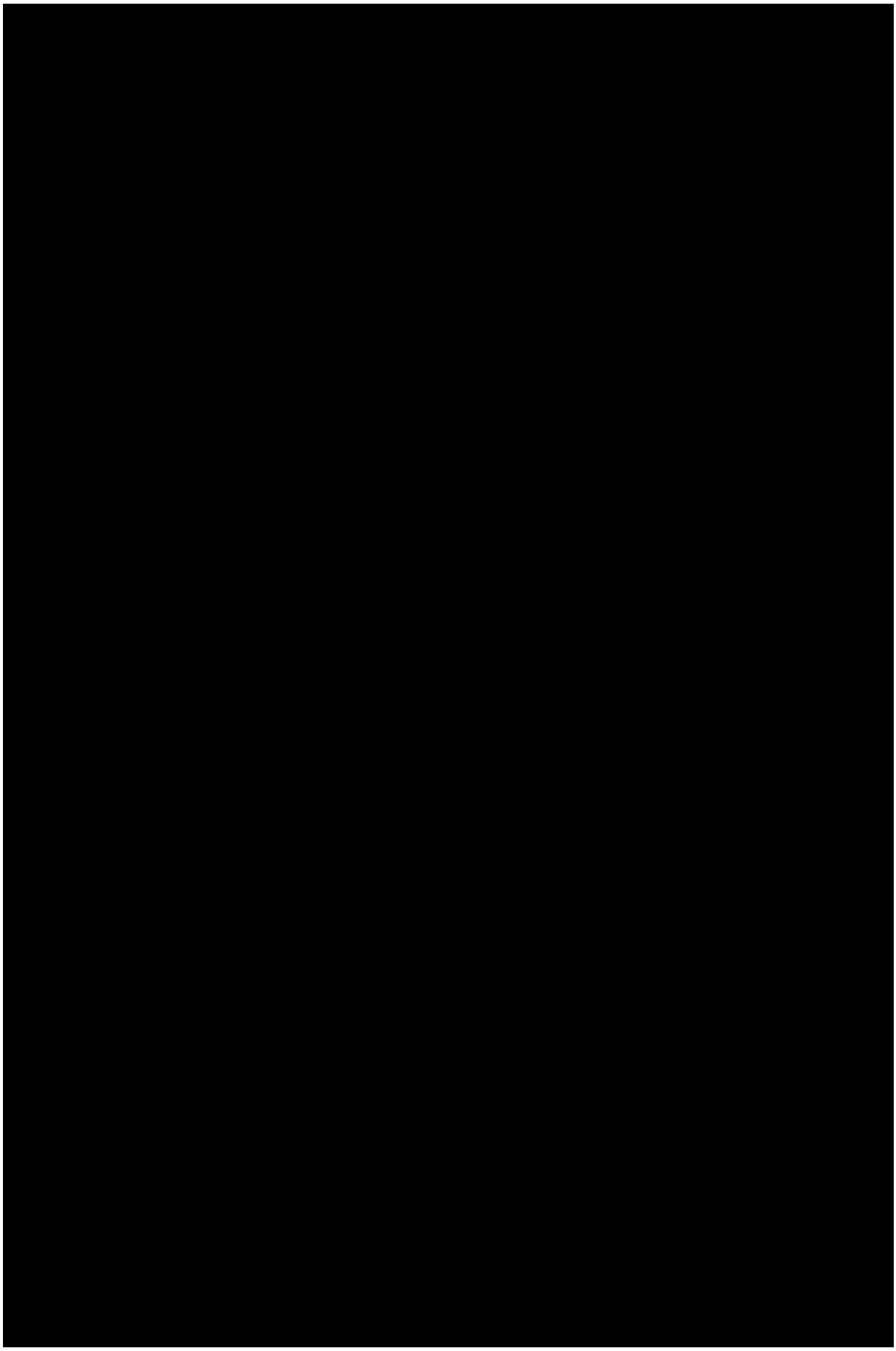
Table 4-2. Potential Safety Concerns Based on Drug Class Effects, Biological Mechanism of Action, and Nonclinical Studies

Safety Risk	Description
Immune-related toxicities	Immune-related adverse effects associated with PD-1 blocking agents include pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin reactions, encephalitis, and other immune-related adverse reactions **(including the identified risks of hypothyroidism, colitis, pneumonitis, and myasthenia gravis).**
Infusion-related reactions	**Severe and life-threatening infusion-related reactions have been observed with other anti-PD-1 therapies and may occur with the administration of AMG 404.** Signs and symptoms may include pyrexia, chills, rigors, flushing, urticaria, hypotension, dyspnea, wheezing, headache, back pain, and abdominal pain.
Embryofetal toxicity	**Based on its mechanism of action, AMG 404 may cause fetal harm if administered during pregnancy. Animal studies published in the literatures have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. However, the risk to a fetus following conception by an AMG 404 exposed male, or the risk to a fetus from an AMG 404 exposed male sexual partner of a pregnant woman, is uncharacterized.**

PD-1 = programmed cell death 1; PD-L1 = programmed death ligand 1

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. To mitigate embryofetal toxicity risk, study subject contraception will be required, and pregnancy status will be monitored. Refer to Section **8.4.3** for specific recommendations regarding the mitigation and management of immune-related toxicities, infusion-related reactions, and embryofetal toxicity.

For additional key safety information, refer to the AMG 404 Investigator's Brochure.



[redacted]

Refer to the AMG 404 Investigator's Brochure, [redacted] for further description of key safety information.

5. Objectives, Endpoints and Hypotheses

5.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability and determine the recommended phase 2 dose (RP2D) of AMG 404 in patients with advanced solid tumors	• Dose limiting toxicities (DLTs), treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, and clinical laboratory tests
[redacted]	
Secondary	
• To evaluate the pharmacokinetics (PK) of AMG 404 as a monotherapy [redacted]	• PK parameters of AMG 404 including, but not limited to, maximum observed serum concentration (C_{max}), time to achieve C_{max} (t_{max}), and area under the serum concentration-time curve (AUC)
• To assess the immunogenicity of AMG 404 as a monotherapy [redacted]	• Subject incidence of anti-AMG 404 antibodies
• To evaluate the preliminary antitumor activity of AMG 404 as a monotherapy [redacted]	• Objective tumor response, duration of overall response, progression-free survival, disease control rate (DCR), and duration of stable disease measured by CT/MRI and assessed per modified RECIST 1.1

Exploratory

[redacted]

5.2 Hypotheses

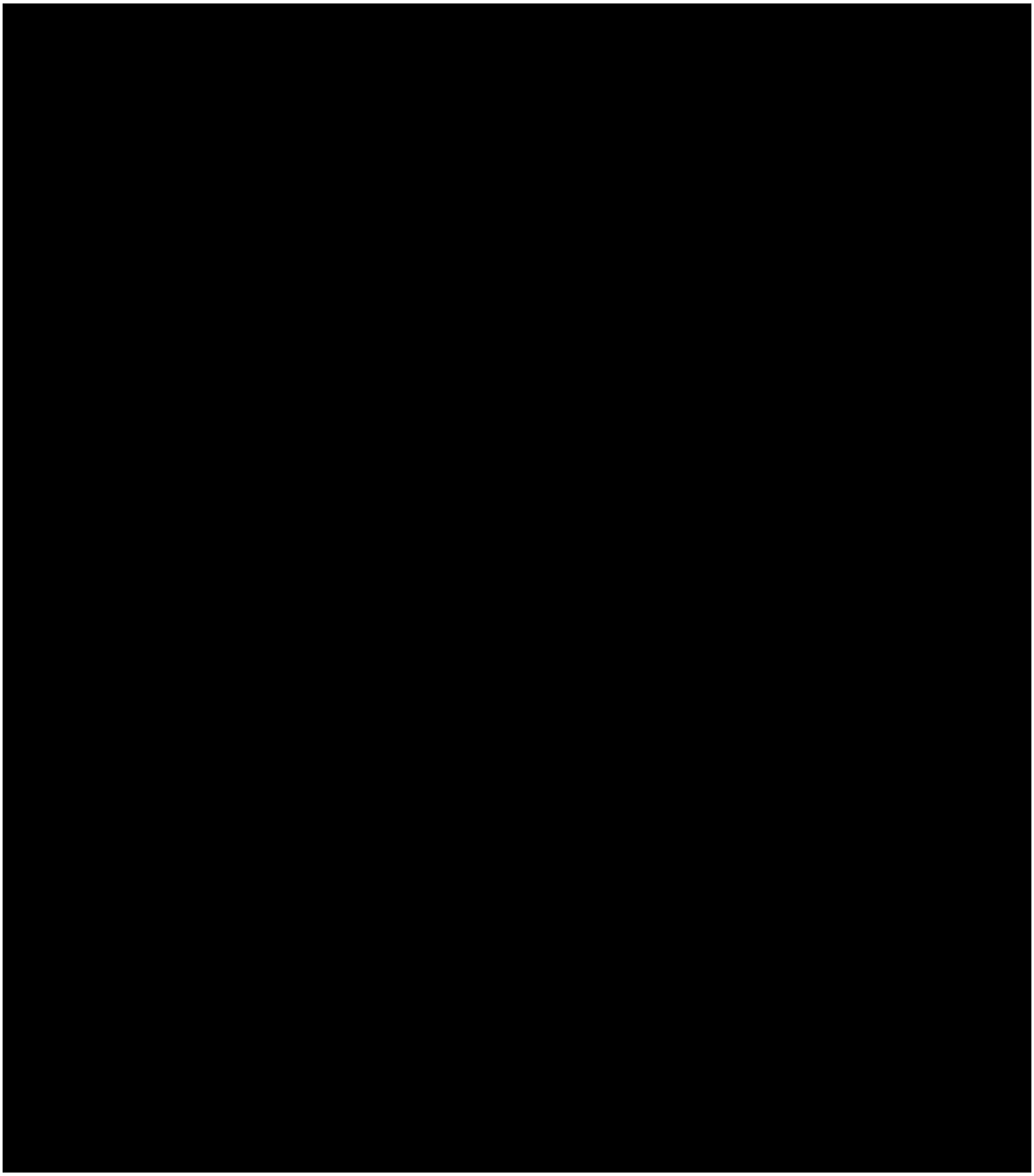
AMG 404, as a monotherapy [redacted] is safe and well tolerated in patients with advanced solid tumors.

6. Study Design

6.1 Overall Design

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of AMG 404 in subjects with advanced solid tumors. The study may be conducted in Australia, United States, France, Poland, United Kingdom, Belgium, Spain, Turkey, South Korea, Taiwan, Japan, Singapore, China, Canada, Brazil and Mexico. Other countries or regions may participate. The study will consist of **up to** 9 cohorts to evaluate the safety, tolerability, PK and PD of AMG 404 administered every 4 weeks (Q4W) with the following doses: Cohort 1 – 240 mg, Cohort 2 – 480 mg, Cohort 3 – Expansion at the dose of 480 mg (subjects enrolled outside of China), Cohort 4 – Exploratory Dose of 1050 mg, Cohort 5 – China/Taiwan/Hong Kong Specific Expansion at the recommended phase 2 dose (RP2D) with a safety lead-in **(**[redacted]**)**, Cohort 6 – Expansion at the RP2D, Cohort 7 – Expansion at the RP2D in specific indications as specified in Section 2.1, Cohort 8 – Expansion at the RP2D in subjects with tumors that are microsatellite

instability-high (MSI-H) or mismatch repair deficient (dMMR), and Cohort 9 – Expansion at the RP2D in subjects with non-small cell lung cancer (NSCLC) that is PD-L1 positive, TPS $\geq$ 50% (Cohorts 6-9 will enroll subjects outside of China).



In Cohorts 1-9, AMG 404 will be administered intravenously (IV) over approximately total 30 minutes, every 4 weeks in subjects with advanced solid tumors. Cohorts 3 and 4 can be opened once Cohort 2 has been completed and determined to be tolerable. Cohorts 5-9 can be opened once the first 6-9 subjects in Cohort 4 have completed the DLT evaluation period and data have been reviewed to determine the RP2D. The DLT

evaluation period will be 28 days. The Dose Level Review Meeting (DLRM) may recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), continuation or delay in dosing, repetition or expansion of a cohort, de-escalation to a lower dose, or termination of the study. Administration of AMG 404 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. For subjects with complete response, treatment beyond 12 months may be permitted upon discussion with the medical monitor. **After discussion with the medical monitor, subjects with complete response, partial response, stable disease or continued clinical benefit at 24 months of treatment, may continue treatment for up to an additional 24 months (up to 48 months of treatment in total).** If a subject completes or discontinues treatment for reasons other than progression, tumor evaluations should continue according to the Schedule of Activities (for Cohorts 1-9, refer to Table 3-1, [redacted] until progression or start of a new treatment regimen.

Cohort 1, 2 and Cohort 4

The doses of 240 mg, 480 mg and 1050 mg will be examined for safety, tolerability, PK, and PD of AMG 404 in subjects with advanced solid tumors. Rules for dose determination, and dose expansion are derived using a modified Toxicity Probability Interval (mTPI) model (Ji et al. 2010) with a target toxicity probability interval (TPI) of 0.20 to 0.33 with a TPI $>$ 0.33 defined as excessive toxicity.

- Subjects will not be dosed at a level above the dose level indicated by the mTPI model. In particular, subjects will not be dosed at the current dose level or higher when the mTPI model indicates stopping enrollment at the current dose level and patients will not be dosed at an escalated dose level when the mTPI indicates staying at the current dose level.
- After reviewing a broad range of safety information including vital signs, laboratory values and detailed adverse events profiles, the team may choose to dose subjects below the dose level indicated by the mTPI model. For example, the team may choose to stop enrollment at the current dose level even if the mTPI model indicates staying at the current dose level.

The Dose Level Review Team (DLRT) will review data, monitor safety, and make recommendations on dose modifications based on all subjects that have been enrolled. A Dose Level Review Meeting will be conducted after Cohorts 1, 2 and 4 and may convene ad hoc to review safety data if deemed necessary.

Three dose levels are planned to be tested:

- Cohort 1: 240 mg every 4 weeks (N = 2-4)
- Cohorts 2 and 3: 480 mg every 4 weeks (Cohort 2: N = 6-9; Cohort 3: N = 20)
- Cohort 4: 1050 mg every 4 weeks (N = 20)

Dose escalation will begin with a run-in dose level of 240 mg (Cohort 1). If no DLTs are observed in Cohort 1, dose escalation will continue to the next planned dose level in Cohort 2. If DLTs are observed in Cohort 1 subsequent will be determined by Amgen after consulting with the Dose Level Review Team (DLRT) and constrained by the mTPI model.

The table below shows rules for dose determination and dose expansion per the mTPI model.

Table 6-1. Guideline for Dose Level Decisions for Cohort 2 (480 mg) and Cohort 4 (1050 mg)

	Number of DLT observed at current dose		
No. of Subjects	**ESCALATE[a]**	**STAY AT CURRENT DOSE**	**STOP ENROLLMENT AT CURRENT DOSE**
3	N/A	≤ 1	≥ 2
4	N/A	≤ 1	≥ 2
5	N/A	≤ 2	≥ 3
6	0	1 – 2	≥ 3
7	≤ 1	2 – 3	≥ 4
8	≤ 1	2 – 3	≥ 4
9	≤ 1	Maximum sample size reached	Maximum sample size reached

[a] For Cohort 4 (1050 mg), if the rules for dose escalation are met, enrollment may be stopped as there is sufficient evidence that 1050 mg dose is safe and tolerable; and this is the highest planned dose level being investigated on study.

Cohort 3

Upon completion of Cohort 2 of the study and depending on data obtained, dose expansion may proceed with the planned dose of 480 mg in Cohort 3 (N = 20) outside of China.

Cohorts 5-9

Upon completion of the first 6-9 subjects in Cohort 4 of the study and depending on data obtained, dose expansion may proceed with the RP2D in Cohort 5 with a safety lead-in

(from China, and from National Medical Products Administration (NMPA) certified sites in Taiwan and Hong Kong) and Cohorts 6-9 (from all countries participating on the study, excluding China). The RP2D will be determined following review of available data obtained in Cohorts 1 through 4 including safety, tolerability, PK and PD data. [redacted]

Cohort 5 **was** a China/Taiwan/Hong Kong-specific expansion cohort with a safety lead-in at one dose below the RP2D followed by evaluation at RP2D, as appropriate. Up to 12 subjects **would** be enrolled in China and NMPA certified sites in Taiwan, and/or Hong Kong. [redacted]

The overall study design is described by a study schema in Figure 3-1. The endpoints are defined in Section 5.1.

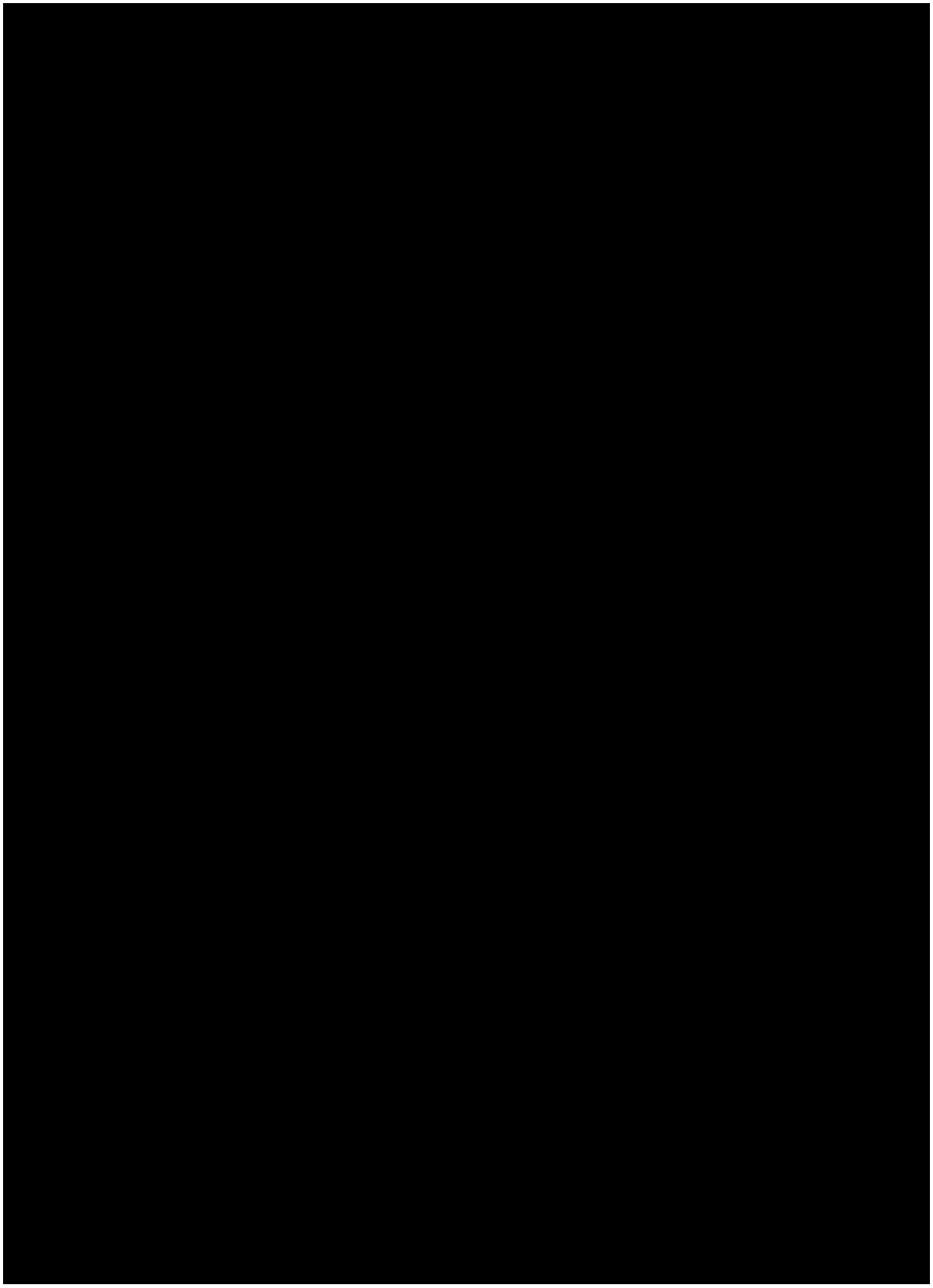
Intra-subject dose escalation for Cohorts 1-9

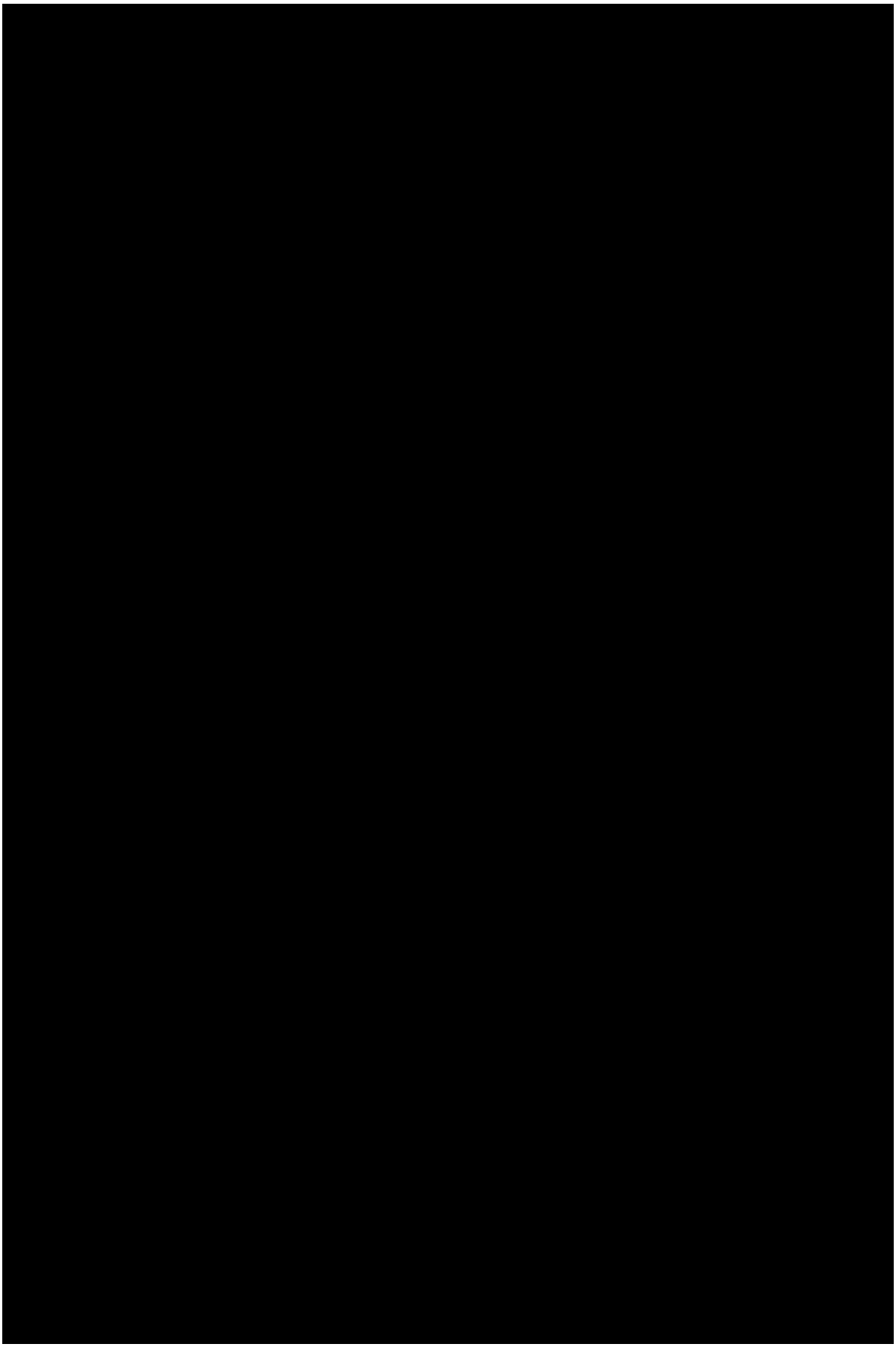
Intra-subject dose escalations are allowed on this study for subjects enrolled, where applicable. Subjects enrolled to Cohort 1 who complete the DLT period may proceed to 480 mg once Cohort 2 has been deemed safe by the DLRT; subjects receiving 480 mg (in Cohorts 1-3) who complete the DLT period may proceed to the RP2D once determined if a dose higher than 480 mg is selected as the RP2D. Subjects enrolled to the safety lead-in dose in Cohort 5, may escalate to the RP2D dose level once the RP2D is determined safe following the China/Taiwan/Hong Kong specific DLRT recommendation. [redacted].

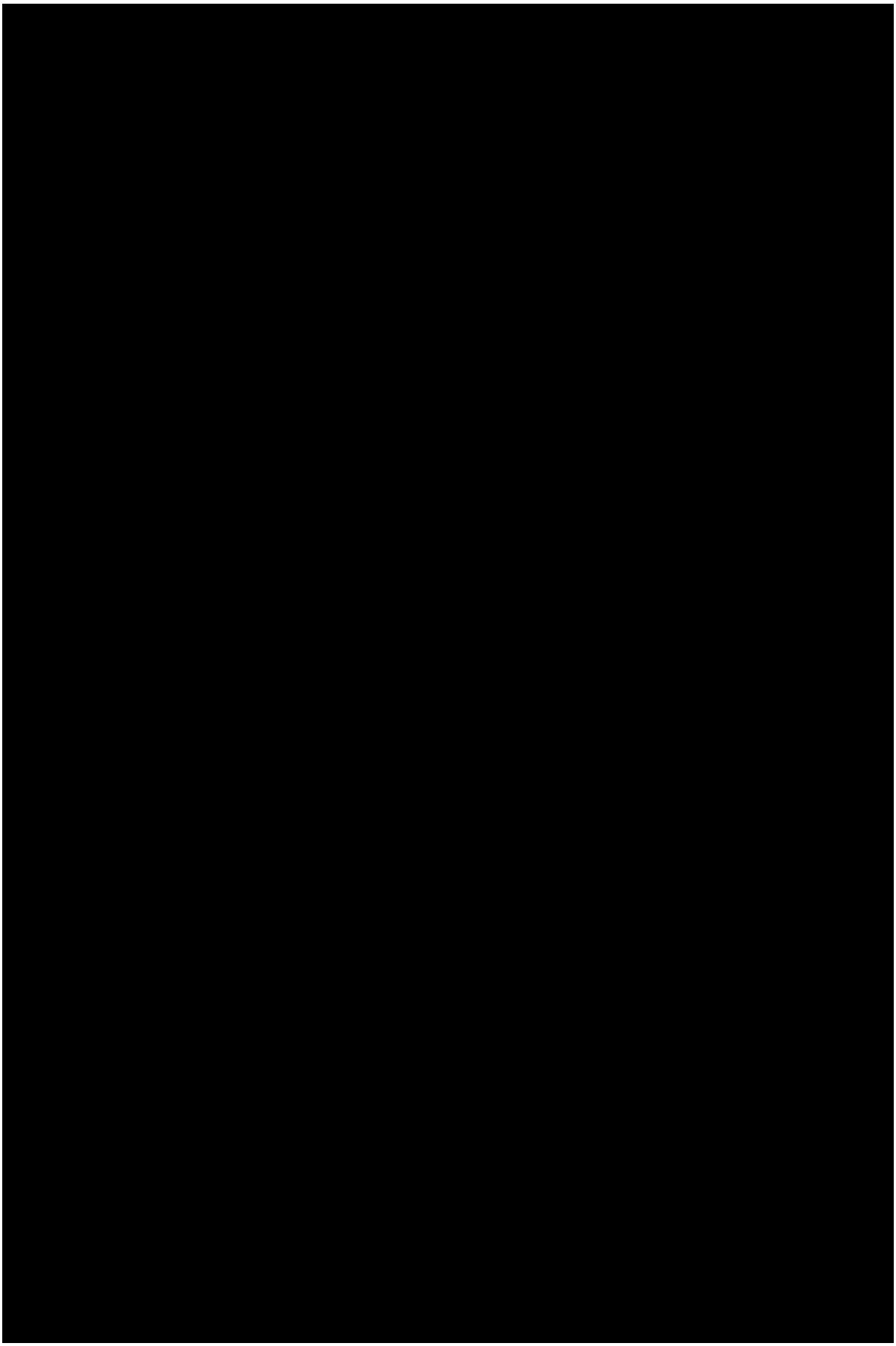
All intra-subject dose escalations may occur after consultation with the sponsor if:

- No DLT has been reported for this subject during or after completion of the DLT period

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







6.2 Number of Subjects

Up to 275 evaluable subjects with advanced solid tumors will be enrolled in the study. Subjects in this clinical investigation shall be referred to as "subjects." For the sample size justification, see Section 11.1.

6.2.1 Replacement of Subjects

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

- Subject who has received at least 90% of the planned dose of investigational product(s) and is followed for at least 1 cycle, or
- Subject who has experienced a DLT;

In addition, for subjects enrolled to Cohorts 7-[redacted] subjects must complete an on-study radiographic assessment.

6.2.2 Number of Sites

Approximately 35 investigative sites in Australia, United States, France, Poland, Turkey, Spain, United Kingdom, Belgium, South Korea, Taiwan, Japan, China, Singapore, Canada, Brazil, Mexico, and other countries or regions may participate in the study.

Sites that do not enroll subjects within 3 months (provided slots are available) of site initiation may be closed.

6.3 End of Study

6.3.1 End of Study Definition

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

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

6.3.2 Study Duration for Subjects

It is anticipated that an individual subject will participate in the study for up to approximately 2.5 years. This includes, the screening period lasting up to 28 days, a treatment period up to 2 years, and a follow up period of 6 months after end of treatment. **Subjects with continued clinical benefit may have their study duration extended for up to 2 additional years of treatment (refer to Section 10.1.3).**

The actual duration for individual subjects will vary depending upon tolerability of study treatment(s), evidence of clinical progression, and willingness to participate in the study.

6.4 Dose Rationale

6.4.1 First in Human Starting Dose Selection Rationale

The PK of AMG 404 was based on allometric scaling of clearance and volume parameters obtained from studies in cynomolgus monkeys. The AMG 404 human PK parameter estimates were comparable to those derived from human population PK models for pembrolizumab and nivolumab (Ahamadi, 2017; Bajaj, 2017). The predicted terminal elimination half-life ($t_{1/2,z}$) is estimated to be consistent with other therapeutic anti-PD1 mAbs. The planned doses of AMG 404 in this study are 240, 480 and 1050 mg administered as short-term IV infusions (approximately 0.5 hours) every four weeks (Q4W) in patients with advanced malignancies. Dose escalation decisions will be guided primarily by observed safety and tolerability of AMG 404,

Dose selection was informed by the clinical experience with other therapeutic anti-PD1 mAbs. Pembrolizumab and nivolumab have been shown to be generally well-tolerated

at and above exposures of their approved doses in patients, which are 200 mg Q3W and 240 mg Q2W, respectively, where flat exposure-response relationships for safety were observed (Chatterjee, 2016; Feng, 2017; Wang, 2017; CDER Clin Pharm Biopharm Review for nivolumab; CDER Clin Pharm Biopharm Review for pembrolizumab). AMG 404 is a human IgG1 anti-PD1 mAb analogue that targets the human PD-1. The fraction crystallizable (Fc) region of AMG 404 has been engineered to eliminate undesired interactions with Fc gamma receptors and complement. In studies with Hut78 T cells and human peripheral blood mononuclear cells, AMG 404 did not have residual antibody-dependent cellular cytotoxicity (ADCC) activity. Taken together, the projected AMG 404 efficacious dose is expected to be well-tolerated. Implementing precautionary measures for AMG 404 as a new molecular entity, a 2-fold safety factor was added to the projected efficacious dose estimate for the starting dose.

To determine the starting dose, efficacious exposure targets for AMG 404 were first computed by scaling clinically efficacious exposures (as assessed by the time-averaged concentration over a dosing interval at steady state [$C_{avg,ss}$]) for approved dosing regimens of anti-PD-1 mAbs, pembrolizumab (200 mg Q3W) and nivolumab (240 mg Q2W) (Freshwater, 2017; Zhao, 2017) by the corrections for molecular weight ratios and the ratios of in vitro pharmacological activity for inhibition of human PD-1 binding to PD-L1. In combination with human PK predictions, the efficacious doses of AMG 404 that achieve the predicted $C_{avg,ss}$ exposures were determined to be between 350 and 720 mg Q4W IV using the results of the 2 studies with a mean estimate of 535 mg Q4W IV.

The starting dose of 240 mg Q4W IV was selected using the efficacious dose estimate of 480 mg based on both approximately the mean efficacious dose estimate (535 mg Q4W IV) and evaluation of in vitro pharmacological activities of AMG 404 and nivolumab, which is also approved for dosing at 480 mg Q4W IV (Prescribing information for Opdivo®) and addition of the 2-fold safety factor. By starting one dose level below the predicted efficacious dose, exposure of subjects to doses that are not expected to be efficacious is limited. Receptor occupancy (RO) data were not utilized for FIH dose selection given that saturated receptor occupancy of other therapeutic anti-PD1 mAbs was observed at subtherapeutic doses in patients.

The starting dose is also supported by the 28-day GLP nonclinical toxicology study in cynomolgus monkeys. AMG 404 has been well-tolerated at doses up to 100 mg/kg QW. At the predicted human exposures of proposed starting dose, exposure multiples for

AUC and C_{max} are calculated to be 24- and 23-fold, respectively when compared to the AUC and C_{max} at the highest non-severely toxic dose (HNSTD) of 100 mg/kg QW in monkeys.

The highest planned dose is 1050 mg Q4W IV. At this dose, exposure multiples for both AUC and C_{max} are calculated to be 5-fold when compared to the AUC and C_{max} at the HNSTD in monkeys.

A fixed dose regimen was selected for the FIH study given that, for mAb-based therapies, body weight may or may not be a determinant of PK variability (Wang, 2009; Bai, 2012). Use of fixed dosing for AMG 404 is further supported by the flat exposure-response relationships for efficacy and safety of other therapeutic anti-PD1 mAbs, indicating that fixed dosing of AMG 404 is not expected to have a clinically meaningful effect on safety and efficacy. In addition, fixed dosing has logistical advantages including ease of administration, reduced risk of dosing errors, minimal preparation by hospital staff, and reduced patient waiting time.

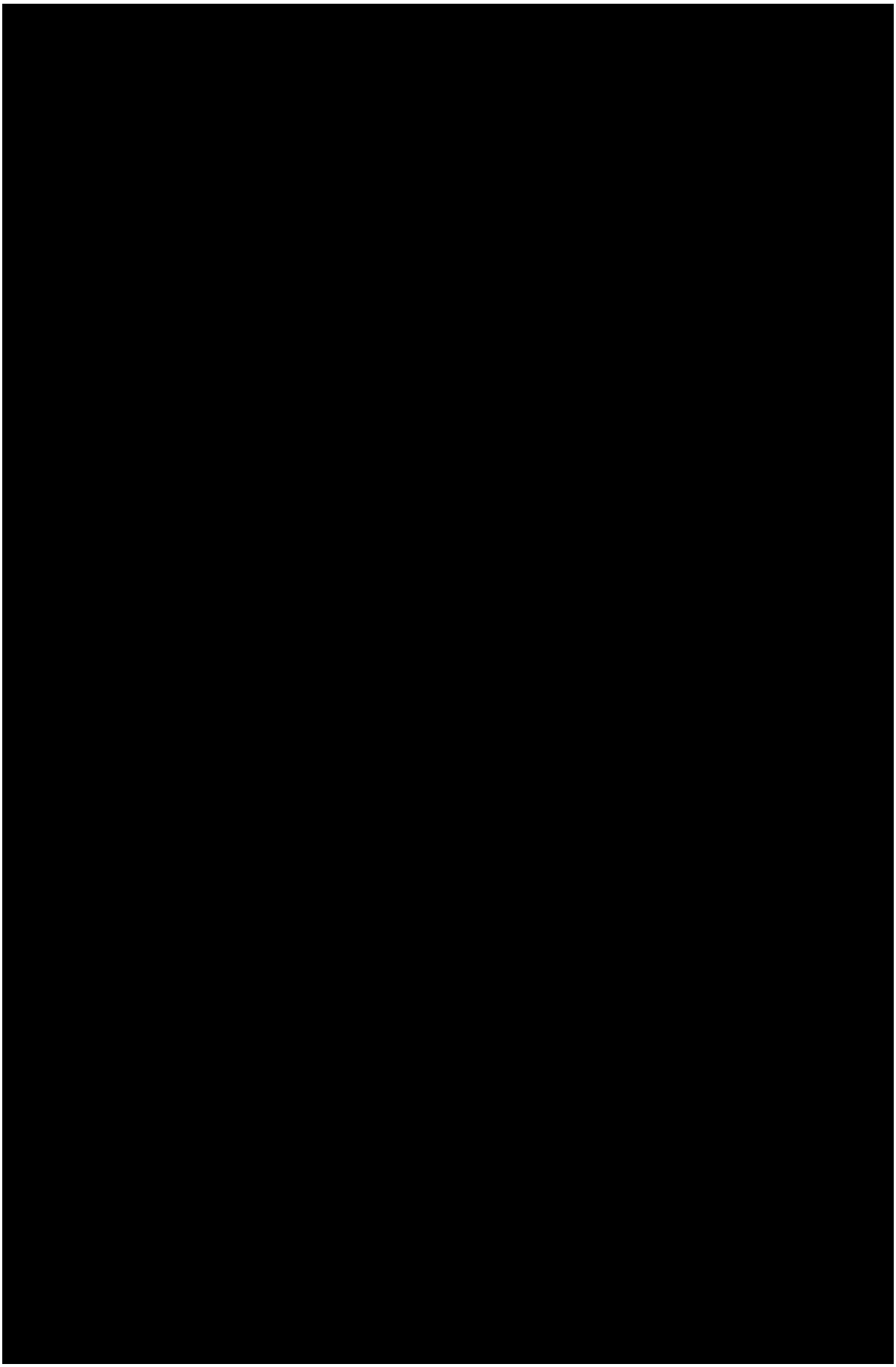
6.4.2 Recommended Phase 2 Dose Selection

Predicted efficacious exposure targets for AMG 404 monotherapy in subjects were computed by scaling clinically efficacious exposures, as assessed by time-averaged concentration over a dosing interval at steady state ($C_{avg,ss}$), for approved dosing regimens of anti-PD-1 mAbs as described above in Section 6.4.1. Using preliminary human PK parameter estimates from population PK modeling of observed data from the study, the efficacious monotherapy dose of AMG 404 that achieves the computed exposure target is predicted to be within range of 480 mg IV Q4W, which is the cohort-2 dose.

Safety, tolerability, PK, and PD of AMG 404 at dose levels of 240, 480, and 1050 mg are being investigated in subjects with advanced solid tumors. As of 08-October-2019 data cut-off date, AMG 404 was safe and well tolerated across the 240- and 1050-mg dose range with no dose-related increases in frequency or severity of adverse events in subjects and no DLTs. Preliminary PK results were consistent with those for other therapeutic anti-PD-1 mAbs. Maximum observed drug concentrations (C_{max}) of AMG 404 occurred at or near the end of infusion with a median t_{max} of 0.5 to 2.5 hours, as expected with 0.5-hour IV infusion administration. An approximately dose-proportional increase was observed over the dose range of 240 to 1050 mg IV Q4W with ~5-fold increases in exposure for both C_{max} and AUC for a 4.4-fold increase in AMG 404 dose. Peripheral RO data were not expected to provide meaningful information to

assess efficacy of AMG 404, given that saturating peripheral RO has been observed clinically at exposures lower than therapeutic doses of other anti-PD-1 mAbs. However, preliminary PD results at the 240-mg and 1050-mg dose levels were consistent with the expected saturation of RO for these doses given the potent inhibition of PD-1/PD-L1 interactions in vitro with low nanomolar IC_{50} values and preliminary observed AMG 404 exposures in human subjects. As of the data cutoff date, 6/36 (16.7%) subjects with postbaseline results are positive for binding ADAs. Of the 6 binding ADA-positive subjects, 5 were in the 480 mg cohort and 1 was in the 1050 mg cohort. Of the 5 binding ADA-positive subjects in the 480 mg cohort, 1 subject had pre-existing binding ADAs and the rest were treatment-emergent. 3/5 of the binding ADA-positive subjects in the 480 mg cohort had an ADA response that was transient. The 1 binding ADA-positive subject in the 1050 mg cohort had treatment-emergent ADA that was sustained at SFU. All of the binding ADAs observed in this study as of the data cutoff date were of low magnitude, with no impact on exposure and have no association with clinical sequelae.

Taking into consideration cumulative preliminary safety data PK, PD, and ADA data, the AMG 404 recommended phase 2 dose for monotherapy is 480 mg IV Q4W in subjects with advanced solid tumors. The efficacious monotherapy dose of AMG 404 is predicted to be within range of this dose.



[redacted]

6.5 Patient Input on Study Design

No patient input was obtained for the design of this study.

7. Study Population

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

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 13.3).

7.1 Inclusion Criteria

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

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

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

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

104 Subject must have histologically or cytologically confirmed metastatic or locally advanced solid tumors not amenable to curative treatment with surgery or radiation. Additionally, for:

- Cohort 7: subject must have a tumor as specified in the Study Schema (Section 3.1)
- Cohort 8, [redacted]: subject must be MSI-H or MMR-deficient

- Cohort 9: subject must have NSCLC, PD-L1 positive, TPS ≥ 50%; not have EGFR or ALK or ROS1 genomic tumor aberrations and may not have received prior systemic treatment for the advanced disease (prior neoadjuvant, adjuvant, or concurrent chemoradiation is allowed).

[redacted]

105 At least 1 measurable lesion as defined by modified RECIST 1.1 which has not undergone biopsy within 3 months of the screening scan. This lesion cannot be biopsied at any time during the study. Note: If there is only one lesion available for biopsy and radiographic assessment, it may be permitted to be biopsied after discussion with sponsor.

106 Subjects with treated brain metastases are eligible provided they meet the following criteria:

- Definitive therapy was completed at least 2 weeks prior to enrollment.
- No evidence of radiographic CNS progression or CNS disease following definitive therapy and by the time of study screening. Patients manifesting progression in lesions previously treated with stereotactic radiosurgery may still be eligible if pseudoprogression can be demonstrated by appropriate means and after discussion with the medical monitor.
- Any CNS disease is asymptomatic, any neurologic symptoms due to CNS disease have returned to baseline or are deemed irreversible, the patient is off steroids for at least 7 days (physiologic doses of steroids are permitted), and the patient is off or on stable doses of anti-epileptic drugs for malignant CNS disease.

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

108 Hematologic function, as follows without growth factor support within 2 weeks prior to study day 1:

- Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L
- Platelet count ≥ 75 x 10^9/L
- Hemoglobin ≥ 9 g/dL (90 g/L)

109 Adequate renal laboratory assessments, as follows:

Estimated glomerular filtration rate based on MDRD (Modification of Diet in Renal Disease) calculation ≥ 60 ml/min/1.73 m^2 for Cohorts 1, 2, 4, 5, and [redacted].
Estimated glomerular filtration rate based on MDRD (Modification of Diet in Renal Disease) calculation ≥ 45 ml/min/1.73 m^2 for Cohorts 3, 6, 7, 8, 9, [redacted].

110 Hepatic function, as follows:

- Total bilirubin ≤ 1.5 x ULN or ≤ 3 x ULN for subjects with liver metastasis

- AST ≤ 3 x ULN or ≤ 5 x ULN for subjects with liver metastasis
- 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 (Note: elevated alkaline phosphatase is acceptable if it is due to non-hepatic associated pathology [eg, bone disease]).

111 Cohort 5 only: Subject is a resident in China, Taiwan, or Hong Kong.

[redacted]

7.2 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 (exception: benign asymptomatic tumors are permitted).

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 ≥ 2 years before enrollment and felt to be at low risk for recurrence by the treating physician.
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated cervical carcinoma in situ without evidence of disease.
- Adequately treated breast ductal carcinoma in situ without evidence of disease.
- Prostatic intraepithelial neoplasia without evidence of prostate cancer.
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ.
- Other malignancies which do not require systemic therapy, may be considered upon discussion with the medical monitor.

203 History of solid organ transplantation.

204 Major surgery within 28 days of study day 1.

Prior/Concomitant Therapy

205 Prior treatment with anti-programmed death 1 (PD-1), anti-PD-L1, CTLA-4 or other checkpoint inhibitor drugs ([redacted]).

206 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.

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. Corticosteroids with no or minimal systemic effect (such as topical or inhalation) are permitted.

Note: Corticosteroids > 10 mg prednisone used for management of contrast allergy for study scans is allowed

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 interstitial lung disease or active, 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 for Human Immunodeficiency Virus (HIV).

214 Has known active Hepatitis B (eg, hepatitis B antigen [HBsAg] reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).

215 Subject currently has an active infection requiring systemic therapy

216 Active or history of any autoimmune disease or immunodeficiencies. Subjects with Type I diabetes, 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 antiarrhythmic 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.

Other Exclusions

219 Males and females of reproductive potential who are unwilling to practice highly effective methods of birth control while on study through 6 months (females) and 8 months (males) after receiving the last dose of AMG 404, [redacted] See Section 13.6 for additional details regarding contraception requirements).

220 Females with a positive pregnancy test.

221 Females who are lactating/breast feeding or planning to breastfeed while on study through 6 months after receiving the last dose of study drug.

222 Females planning to become pregnant while on study through 6 months after receiving the last dose of the study drug.

223 Males unwilling to abstain from donating sperm during treatment and for an additional 8 months after the last dose of AMG 404, [redacted]

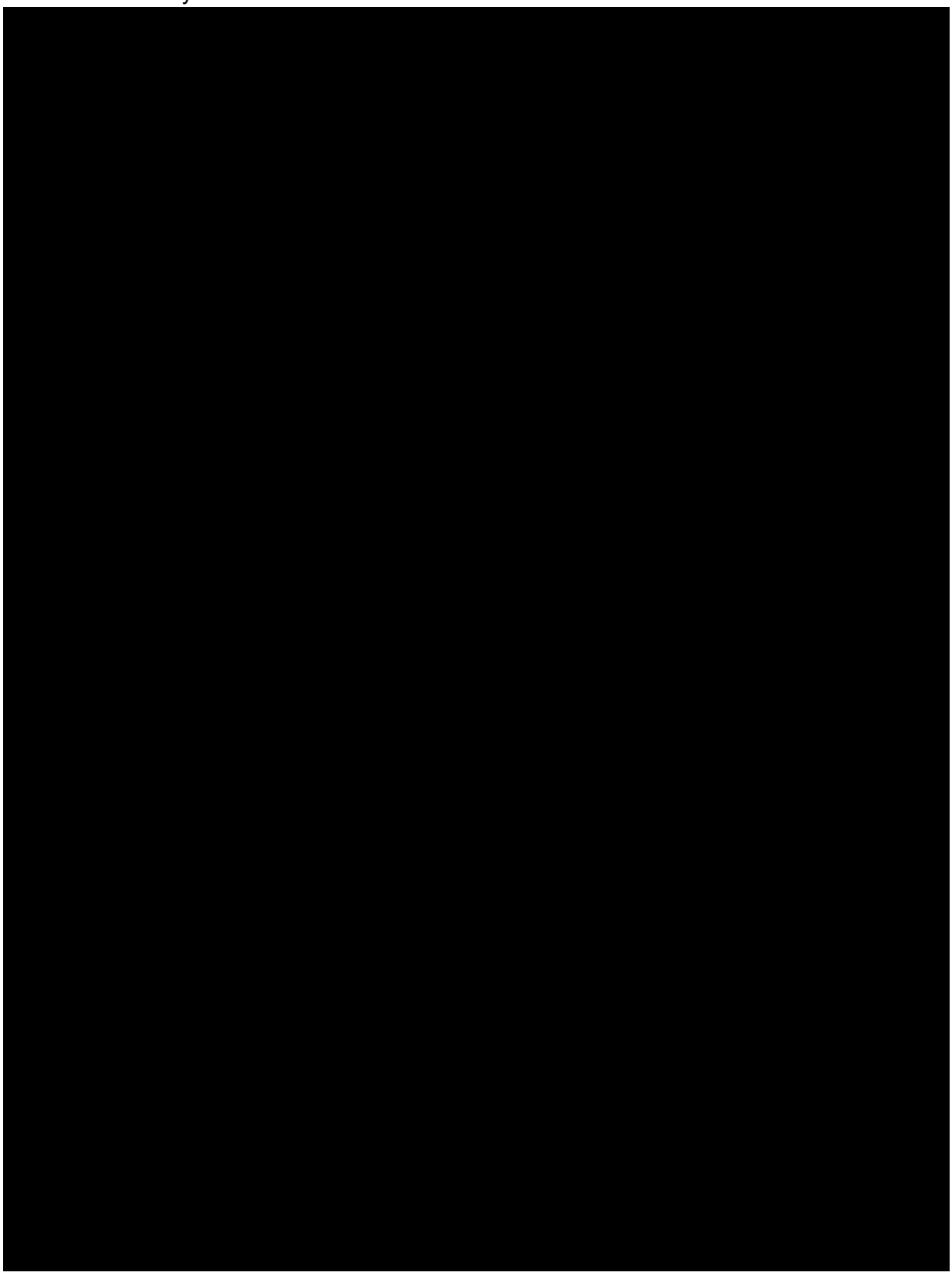
224 Subject has known sensitivity to any of the products or components to be administered during dosing.

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.

227 Subjects with known sensitivity to any of the products to be administered during the study.



7.3 Subject Enrollment

All screening tests and procedures should be performed within 28 days prior to study day 1, unless otherwise indicated. All blood and urine samples collected for screening assessments will be submitted and analyzed by the local laboratory. Time permitting, screening laboratory assessments used to determine subject eligibility may be repeated if necessary.

Subjects who do not meet eligibility criteria within the 28 day screening period will not be eligible for enrollment. Subjects may be re-screened up to 3 additional times at the discretion of the investigator. The subject must be re-consented if a re-screening attempt occurs outside of the 28 day screening period. Subjects who are deemed ineligible will be documented as screen failures.

An Amgen representative will notify the site in writing when a cohort is open to screen and enroll subjects. Subjects may be eligible to enroll once all screening tests and procedures are completed and results indicate that all eligibility criteria are met. A site representative will complete and send the enrollment eligibility worksheet to Amgen accompanied with medical history, treatment history for the disease being investigated and list of current medications. The eligibility worksheet and accompanying information should be completed and emailed to the Amgen representative at least 3 days prior to the planned day of first dose. The Amgen representative will acknowledge receipt of the paperwork and send confirmation of the cohort and dose level assignment for the subject.

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

7.4 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 10.1.1.

8. Treatment Procedures

All investigational and non-investigational products must be prepared and administered by a qualified healthcare professional. Subjects should be assessed clinically for adverse events/ toxicity prior to each dose using the CTCAE version 5.0. Complete blood count with differential and chemistry panels including liver enzyme laboratory tests (ALT and AST) and total bilirubin should be obtained according to the Schedule of Activities (section 3.2) and the results should be checked within 2 days prior to each dose of treatment.

The treatment cycle interval may be increased due to toxicity. If a subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) as supportive care, AMG 404 dosing must be held until the corticosteroid dose has decreased to < 10 mg prednisone daily (or equivalent). [redacted]

8.1 Investigational and Non-investigational Products

8.1.1 Investigational Product: AMG 404

AMG 404 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

[redacted]

The investigational product will be dispensed at the research facility by a qualified staff member.

At the beginning of a treatment cycle a physician or nurse trained in emergency medical care must be available when the infusion of investigational product is started for immediate intervention in case of complications.

AMG 404 will be delivered using infusion pumps approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment.

AMG 404 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines.

The drug will be administered as an IV infusion at a constant flow rate over 30 minutes.

For Cohorts 1-9, each cycle of AMG 404 will be 28 days in length. Subjects will receive 240 mg, 480 mg or 1050 mg of AMG 404 depending on the cohort the subject is enrolled into. All subsequent doses will be administered every 28 days (± 3 days). [redacted] [redacted].

[redacted]

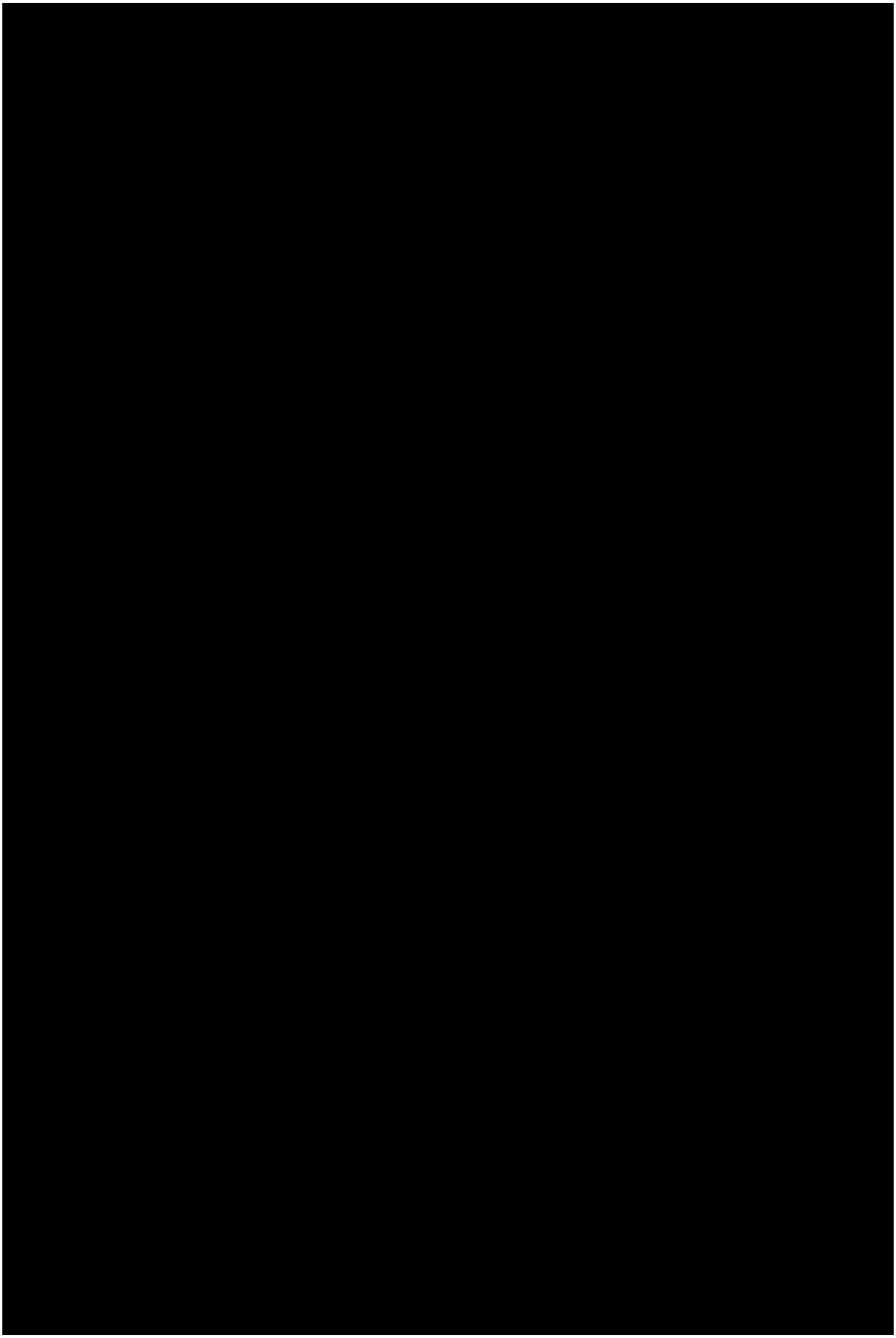
All safety assessments must be performed within 2 days prior to start of cycle. Assessments should be performed as indicated in the Schedule of Activities (see section 3.2). AMG 404 may be withheld or discontinued as necessary for safety reasons.

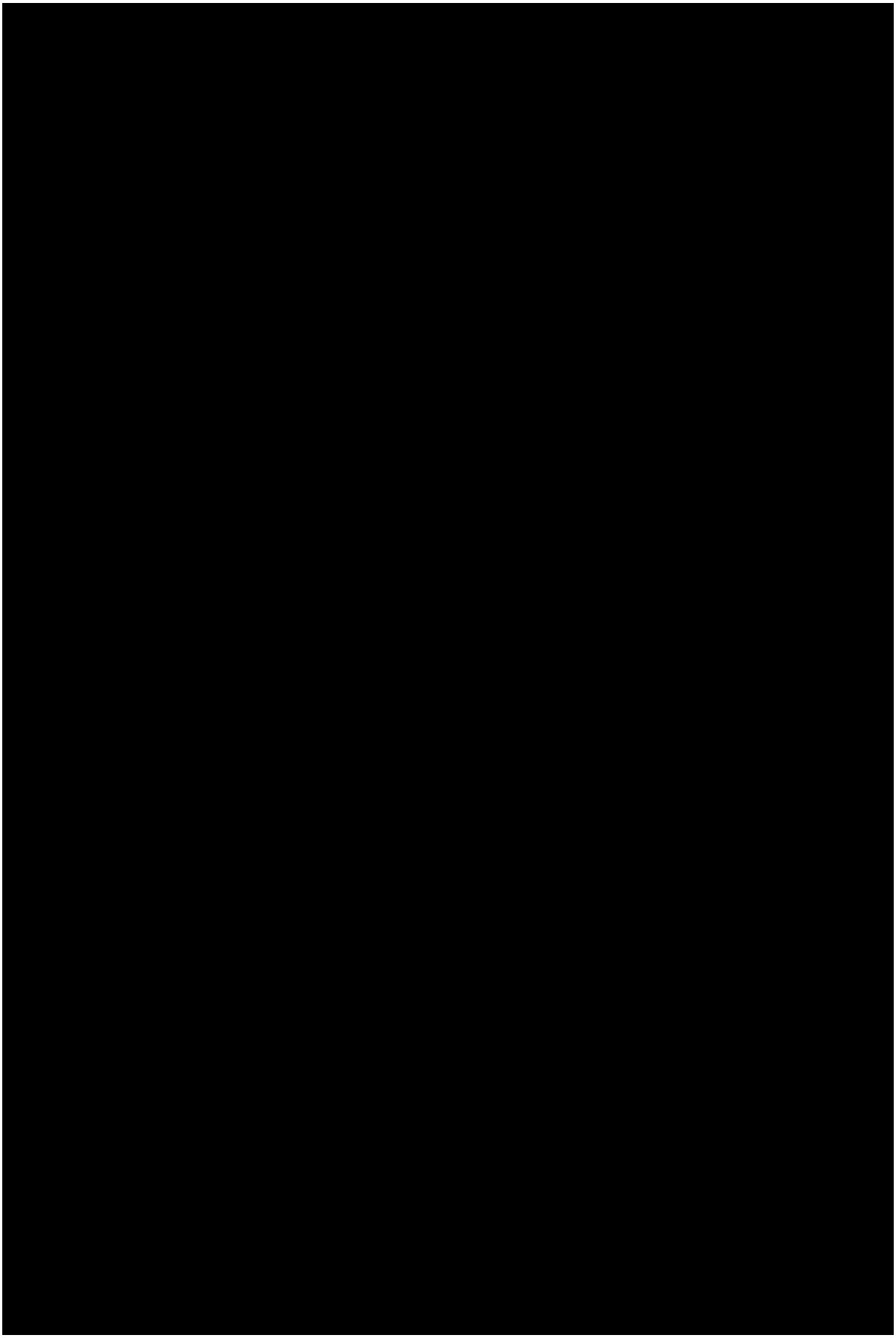
8.1.2 Cohorts 1-9 Investigational Product

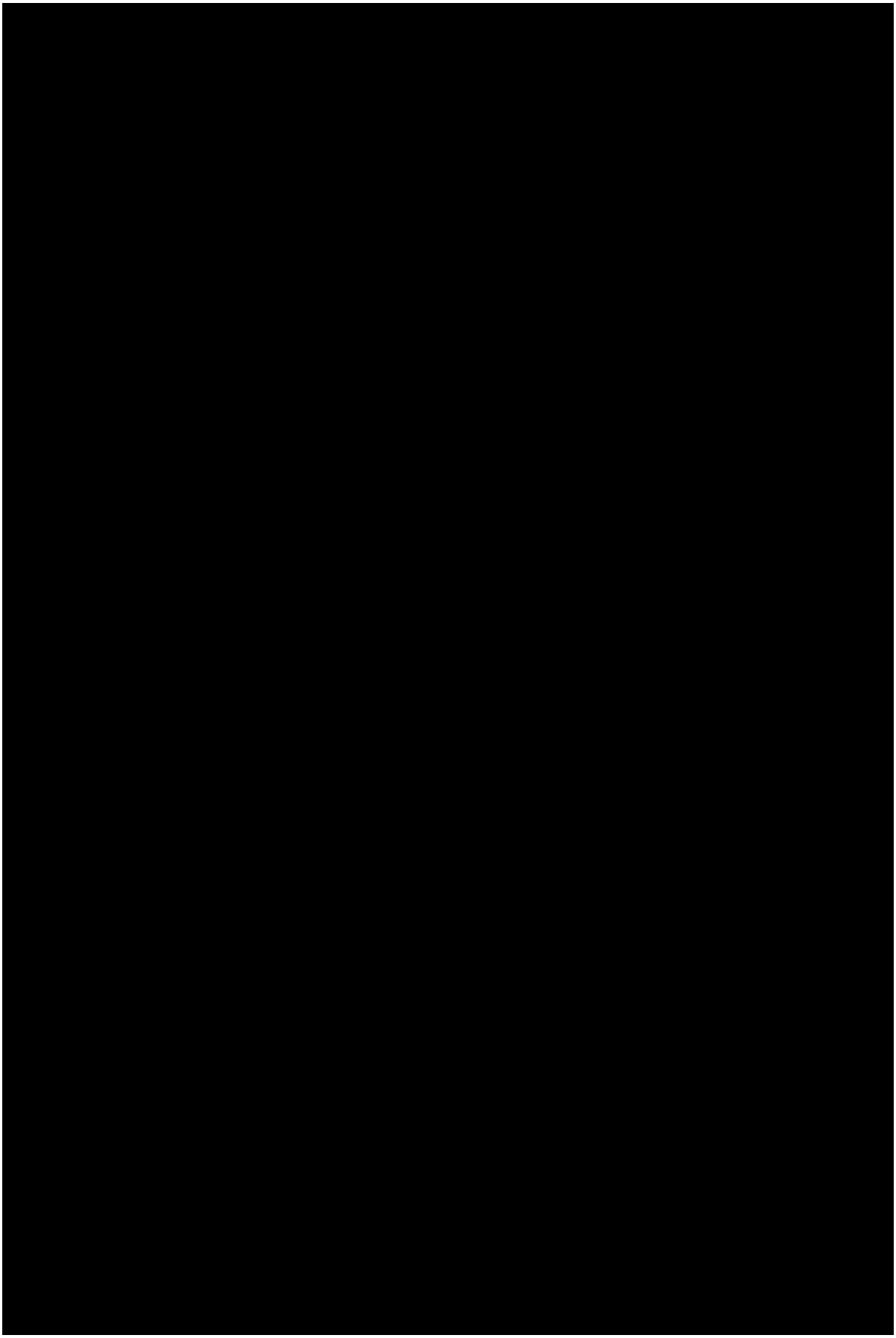
[redacted]

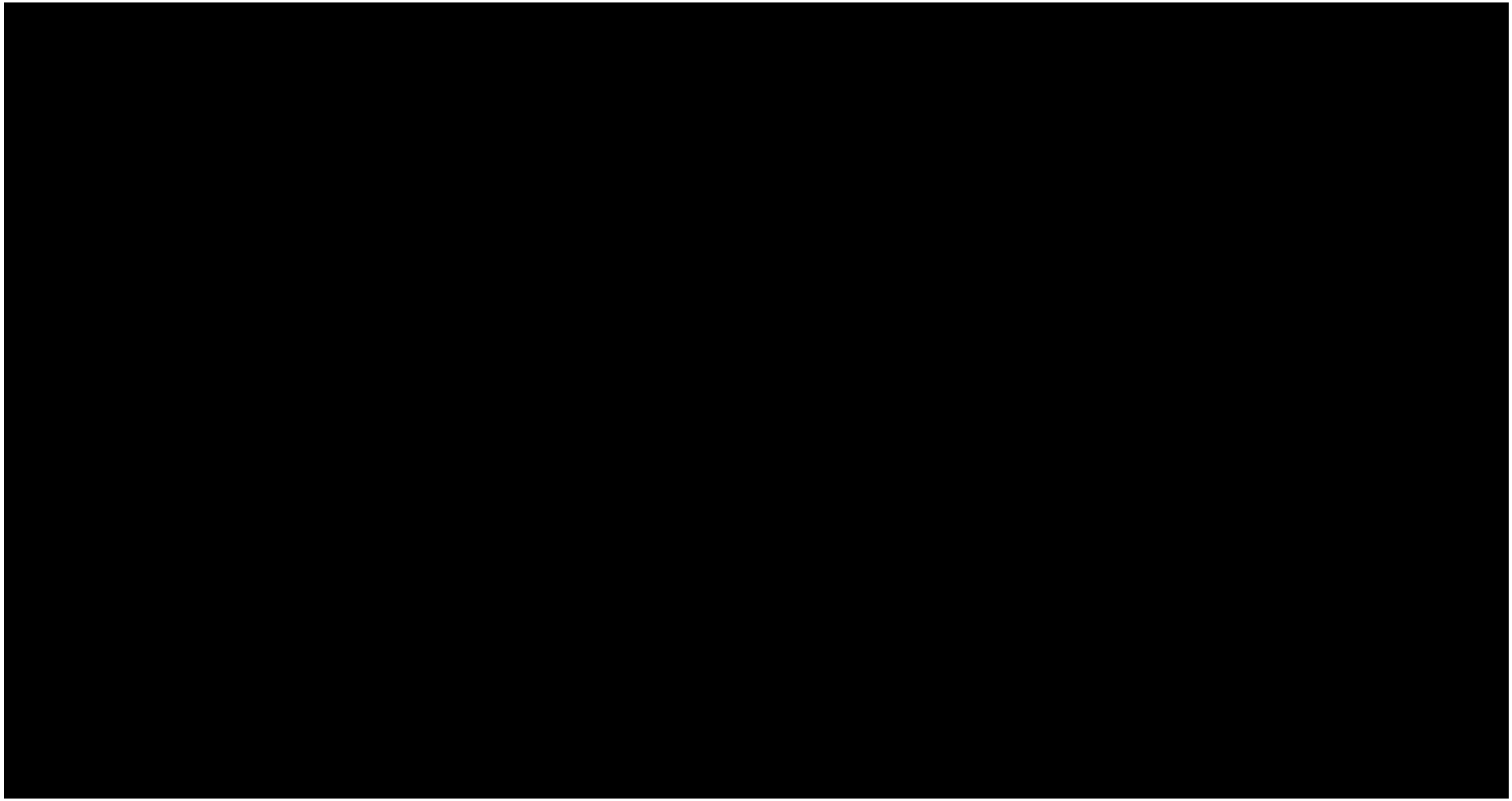
Table 8-1. Cohorts 1-9 Investigational Product: AMG 404

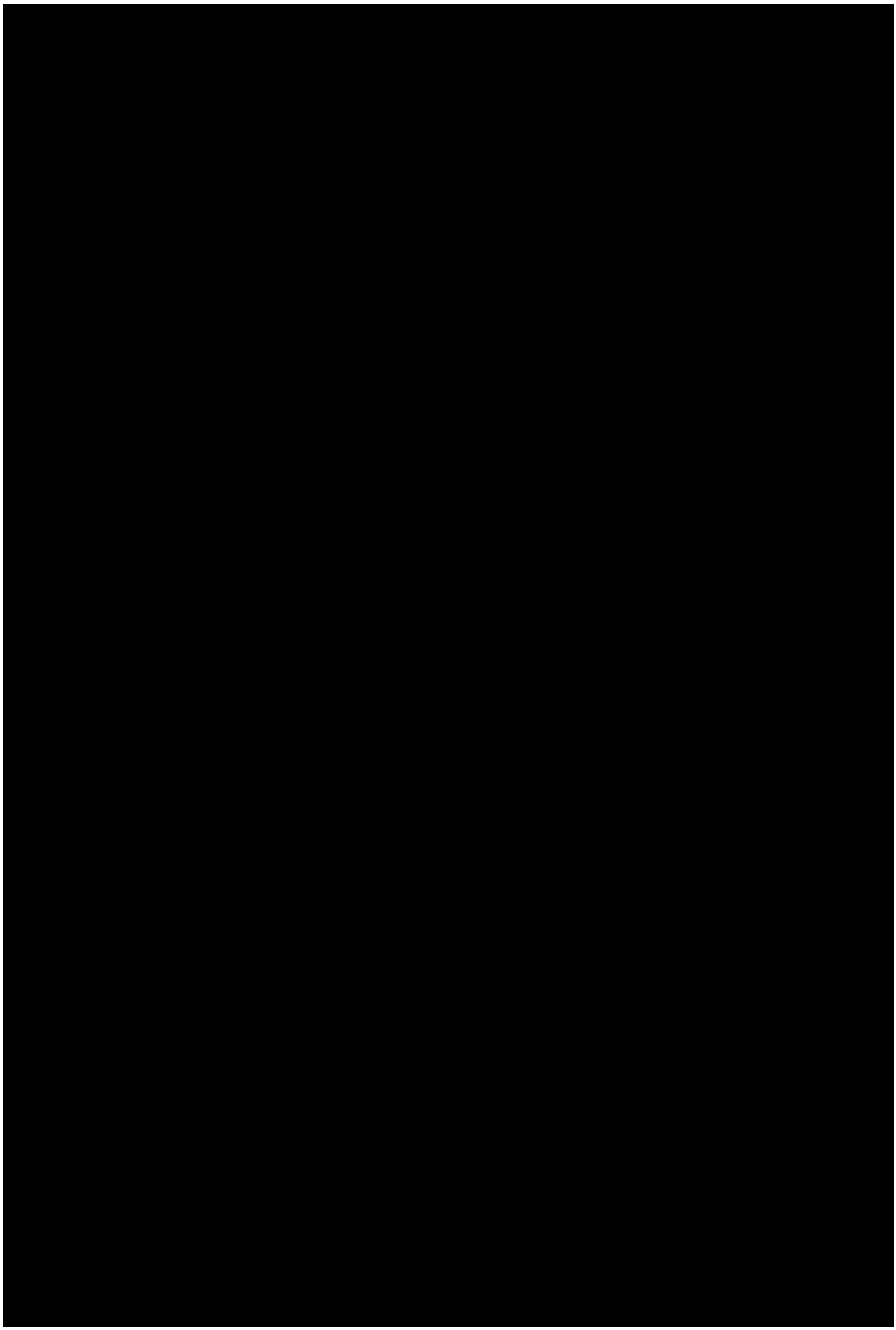
[redacted]











[redacted]

8.1.7 Medical Devices

There are no investigational medical devices being used in this study.

Investigational product must be administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment in the outpatient setting. Investigational product solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines that are both compatible with the investigational product. Other non-investigational medical devices may be used in the conduct of this study as part of standard care. Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

8.1.9 Other Treatment Procedures

There are no other treatment procedures in this study.

8.1.10 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational/non-investigational product(s) provisioned and/or repackaged/modified by Amgen. AMG 404 [redacted] are the investigational products in this study.

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

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

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

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

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

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

Administration of systemic corticosteroids (AMG 404 must be discontinued if ≥ 10 mg per day prednisone or equivalent is continued for more than 12 weeks), immunomodulators, and hormonal replacement therapy for the management of toxicities (eg, immune-related adverse events) is allowed. Corticosteroids with no or minimal systemic effect (eg, topical, inhalation) are allowed ([redacted]).

Any live vaccine therapies for the prevention of infectious disease are excluded.

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 an investigational study (drug or device) within 21 days of study day 1
- Major surgery within 28 days of study day 1
- Enrollment into another investigational drug or device study

8.2 Method of Treatment Assignment

Subjects who meet the eligibility criteria will be assigned to treatment with AMG 404. The treatment assignment date is to be documented in the subject's medical record and on the enrollment CRF.

8.3 Blinding

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

8.4 Dose Modification

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

Planned DLRMs will be held to review data, monitor safety, and recommend dose changes or other necessary actions, on a per cohort basis. Considering each cohort independently, a DLRM will occur after the required DLT-evaluable subjects have completed the DLT window:

- All in Cohorts 1 and 2
- The first 6-9 subjects of Cohort 4
- [redacted]
- Ad hoc if deemed necessary by the Medical Monitor

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

The China/Taiwan/Hong Kong specific DLRT will be composed of the investigators in China/Taiwan/Hong Kong or designee, Amgen Medical Monitor, Amgen Global Safety Officer or designated safety scientist, Amgen Early Clinical Development Manager, and Biostatistics representative. Additional members may be added as needed (eg, Clinical Pharmacologist).

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), Amgen Medical Monitor, and the Amgen Global Safety Officer or delegate must be in attendance for DLRM to proceed. The DLRM will be rescheduled if a quorum is not reached.

Voting members of the DLRM will include the Amgen Medical Monitor, the Amgen Global Safety Officer or designated safety scientist, and all actively screening and enrolling investigators or their qualified sub-investigator designee. For cohorts with dosing decisions, the team may recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), continuation or delay in dosing, repetition or expansion of a cohort, de-escalation to a lower dose, or termination of the study. Intra-subject dose escalation is allowed, where applicable. When the subject completes the DLT period the subject may proceed to 480 mg for the following treatment cycle once Cohort 2 has been deemed safe by the DLRT; subjects receiving 480 mg (Cohorts 1-3) who complete the DLT period may proceed to the RP2D once determined if a dose higher than 480 mg is selected as the RP2D. Subjects enrolled at the safety lead-in dose in Cohort 5 may escalate to the RP2D once deemed safe by the China/Taiwan/Hong Kong specific DLRT. All intra-subject dose escalations may occur after consultation with the sponsor as described in Section 6.1. The Amgen Medical Monitor and Global Safety Officer 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 404 to allow the dose level modification and/or cohort continuation/expansion to proceed. All available study data including demographics, medical history, concomitant medications, AEs, electrocardiograms (ECGs), vital signs, laboratory results, and emerging PK or pharmacodynamics data will be reviewed. Data to be reviewed may be unqueried.

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

8.4.2 DLT Definition

The DLT window (ie, DLT-evaluable period) will be the first 28 days of AMG 404 treatment (starting cycle 1, day 1) for Cohorts 1-9. [redacted] The DLT window may also be extended to assess events starting within the window in case the DLT definition is time dependent.

The subject will be DLT evaluable if the subject has completed the DLT window as described above**,** or experienced a DLT any time during the DLT window, or has received at least 90% of the planned dose of investigational product(s) and is followed

for at least 1 cycle. A subject will not be DLT evaluable if he/she drops out before completion of the DLT-evaluable period for reasons other than a DLT. All available safety data for subjects who are not DLT-evaluable will still be evaluated and considered in DLRT recommendations (see also Section 13.3).

See Section 6.2.1 for description of replacement of subjects.

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

- Any treatment related grade 5 toxicity
- Grade 4 neutropenia or thrombocytopenia > 7 days in duration
- Febrile neutropenia
- Grade 4 anemia
- Grade 3 or 4 non-hematologic toxicity, with the following exceptions:
  - DLT Exemption: Grade 3 endocrinopathies if manageable with replacement therapy
  - DLT Exemption: Grade 3 nausea/vomiting or diarrhea < 72 hours in the absence of maximal medical therapy
  - DLT Exemption: Grade 3 fatigue < 1 week
  - DLT Exemption: Asymptomatic ≥ grade 3 electrolyte abnormalities that last < 72 hours, is not clinically complicated, and resolved spontaneously or responds to conventional medical interventions
  - DLT Exemption: ≥ Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
  - DLT Exemption: Other select lab abnormalities that do not appear to be clinically relevant or harmful to the patient and/or can be corrected with replacement or modifications (eg, grade 3 lymphopenia, grade 3 hypoalbuminemia)
- Recurrent grade 2 pneumonitis
- Delay in cycle 2 treatment for > 14 days due to an adverse event in the dose escalation portion of the study due to study drug-related toxicity
- Any other toxicity requiring permanent discontinuation of AMG 404 or [redacted] per Table 13-2 and section 8.4.3.2

[redacted]

Cumulative adverse events profile will be taken into consideration when making decisions on dose escalation or de-escalation.

Any subject meeting the criteria for Hy's Law case (ie, severe drug-induced liver injury) will be considered a DLT. A Hy's Law case is defined as: AST or ALT values of ≥ 3 x ULN AND with serum total bilirubin level (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 Table 13-2 on hepatotoxicity management and Section 13.8 for further explanation of Hy's law case and Management of Hepatic Function).

If a subject experiences a DLT during the DLT evaluation period, study treatment should be discontinued for that subject. Additionally, any treatment related toxicity meeting the DLT definition after day 28 should result in discontinuation of therapy, unless Table 13-2 recommends otherwise. In subjects with PR, CR or evidence of clinical benefit (as determined by the investigator), an option to continue at the same or at a reduced dose level can be considered once the toxicity returns to the subject's baseline value or CTCAE grade ≤ 1 if deemed appropriate by the investigator and sponsor.

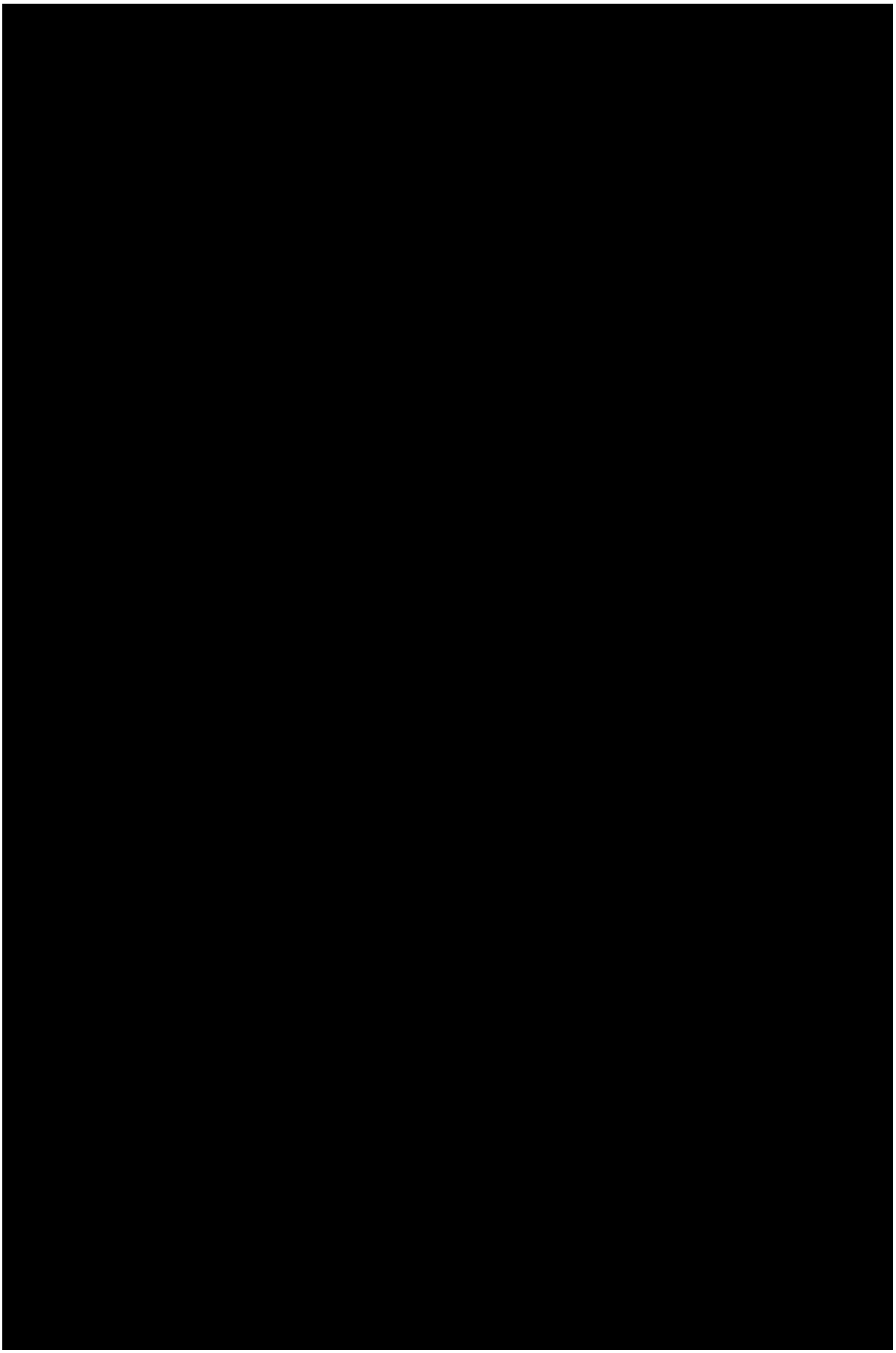
8.4.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

The causality of each adverse event will be assessed individually for each protocol-mandated therapy. [redacted]

8.4.3.1 Amgen Investigational Product: AMG 404

Each subject will stay on the dose level assigned unless treatment needs to be stopped. The reason for dose withholds and dose delays is to be recorded on each subject's CRF. AMG 404 may be temporarily withheld or discontinued as necessary, but a partial dose reduction is not permitted.

[redacted]



[redacted]

8.4.3.4 Immune-related Adverse Reactions

Adverse events following the administration of AMG 404 may represent an immunologic etiology. Based on clinical experience with other anti-PD-L1 therapies, these immune-related toxicities may occur shortly after the first dose to several months after the last dose of treatment and may affect more than one body system simultaneously. Early recognition and management are critical to reduce complications.

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

Based on the type and severity of the immune-related adverse event, withholding or permanent discontinuation of AMG 404, [redacted] may be required, in addition to treatment with corticosteroids and/or other therapies. Dose modification and toxicity management guidelines for immune-related adverse reactions are provided in Table 13-2.

8.4.3.5 Infusion-related Reactions

Infusion-related reactions may occur with the administration of AMG 404. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, rigors, flushing, urticaria, hypotension, dyspnea, wheezing, headache, back pain, and abdominal pain. If an infusion-related reaction is suspected, perform a physical examination, monitor vital signs, monitor pulse oximetry, and perform and ECG if the patient is experiencing chest pain or sustained tachycardia.

For mild or moderate infusion-related reactions, interrupt or slow the rate of infusion. For severe or life-threatening infusion-related reactions, permanently discontinue AMG 404, [redacted] Treatment guidelines for infusion reactions associated with the administration of AMG 404 are provided in Table 13-4. [redacted]

8.4.3.6 Embryo-fetal Toxicity

Based on its mechanism of action, AMG 404 may cause fetal harm if administered during pregnancy. Animal studies have demonstrated that inhibition of the PD-1/PD-L1

pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 6 months (female subjects) or 8 months (male subjects) after the last dose of AMG 404. Refer to Section 13.6 for contraceptive requirements during the study.

Pregnancy testing will be conducted prior to administration of each dose of AMG 404, [redacted] for female subjects of childbearing potential (see section 3.2).

8.4.4 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 13.8 for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

8.4.5 Dose Modification Guidelines for SARS-COV2 Infection

Guidance for dose modifications due to subjects with confirmed SARS-COV2 infection is provided below in Table 8-8.

Table 8-8. Dose Modification Guidelines for SARS-COV2 Infection

	Symptom Severity	Protocol Therapy Modification	Treatment	Discontinuation
SARS-COV2 Infection	Asymptomatic	Withhold treatment for at least 10 days from positive RT-PCR test	Treatment per local standard of care	For treatment delay longer than 6 weeks, discuss with medical monitor
	Mild/Moderate	Withhold treatment until resolution of clinically relevant symptoms and a minimum of 10 days after symptom onset		
	Severe	Withhold treatment until resolution of clinically relevant symptoms and a minimum of 20 days after symptom onset		

RT-PCR = reverse transcription polymerase chain reaction; SARS COV2 = severe acute respiratory syndrome coronavirus 2

8.4.6 Dose Modification Due to Surgery During Study Treatment

Should significant surgery occur during study treatment, in general it is anticipated that study treatment should not be resumed before a 28 day post-operative period. Exceptions to the minimum 28 day post-operative period should be approved by the medical monitor.

[redacted]

8.5 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 Investigational Product Instruction Manual.

8.6 Treatment Compliance

Compliance to treatment and the corresponding assessments should be followed according to the Schedule of Activities (Section 3.2) and the Treatment Procedures (Section 8).

8.7 Treatment of Overdose

AMG 404 Overdose

There is no treatment for overdose of this product. In the event of an overdose, the investigator should contact the Amgen Medical Monitor immediately.

8.8 Prior and Concomitant Treatment

8.8.1 Prior Treatment

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

8.8.2 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 8.1.11.

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

Collected therapy name, indication, dose, unit, frequency, route, start date, and stop date to be recorded in the eCRF.

8.8.2.1 SARS-COV2-Vaccination

Every effort should be made to fully vaccinate subjects prior to 14 days from first dose of investigational product. The use of vaccines except live and live attenuated vaccines will be allowed during therapy per regional and institutional standard of care. However, SARS-COV2 vaccinations should be avoided during screening (within a minimum of 14 days from first dose of IP) and should be also avoided in the first treatment cycle for better assessment of safety parameters. Throughout the trial, SARS-COV2 vaccination

should be avoided within 3 days after the administration of IP. Record SARS-COV2 vaccination as a concomitant medication and collect therapy name, indication, dose, unit, frequency, route, and date of administration.

9. 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 at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 9.1, and 9.2.2.

9.1 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 (Section **3.2**) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined

- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Disease progression
- Pregnancy

9.2 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 13.7 for further details). Refer to the Schedule of Activities (Section 3.2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

This section is not applicable.

9.2.2 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

9.3 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.

10. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Section 3.2).

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.

10.1 General Study Periods

10.1.1 Screening, Enrollment and/or Randomization

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

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

10.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 3.2). The date of the first dose of study drug administration is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date.

10.1.3 Extended Treatment Period

Visits will occur per the Schedule of Activities (Section 3.2). Subjects with complete response, partial response, stable disease or continued clinical benefit at 24 months of treatment, may continue treatment for up to an additional 24 months (up to 48 months of treatment in total) after discussion with the medical monitor. A separate informed consent for extended treatment must be signed.

10.1.4 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, two safety follow-up visits are required. A safety follow-up visit will be performed approximately 30 (+ 3) days after the last administration of study drug, and also 140 days (±7 days) after the last administration of AMG 404. Adverse events should continue to be reported through 140 days (± 7 days) after the last administration of AMG 404.

10.1.5 Long-term Follow-up

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

[redacted]

10.1.6 End of Study for a Particular Study Subject

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

10.2 Description of General Study Assessments and Procedures

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

10.2.1 General Assessments

10.2.1.1 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.

10.2.1.2 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 **may** be used to study the impact of the protocol-required therapy on [redacted] PK.

10.2.1.3 Medical History

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

10.2.1.4 Physical Examination

Physical examination will be performed as per standard of care by the investigator or designee at screening and at the time points specified in the Schedule of Activities (Section 3.2). The physical examination will include general appearance, including examination of the skin, spleen, respiratory, cardiovascular, musculoskeletal, and neurological systems.

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

10.2.1.5 Physical Measurements

Height should be measured without shoes at screening only. Weight should be measured without shoes at the time points specified in the Schedule of Activities (Section 3.2).

10.2.1.6 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 Appendix 8.

10.2.2 Efficacy Assessments

Tumor evaluations (by CT or MRI as appropriate) and tumor markers, if applicable, are to be collected at time points specified in the Schedule of Activities (Section 3.2). Imaging may also be performed more frequently if clinically necessitated at the discretion of the managing physician. Radiographic response (Complete Response, Partial Response) requires confirmation by a repeat, consecutive scan at least 4 weeks after the first documentation of response and may be delayed until the next scheduled scan to avoid unnecessary procedures. Radiographic progression (Progressive Disease) requires confirmation by a repeat, consecutive assessment 4-6 weeks after the first detection of radiological progression. Upon discussion with the Sponsor, in the absence of clinical deterioration and with the subject's consent (subject must sign addendum consent), subjects may continue to receive AMG 404 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 [redacted]). In some circumstances it may be difficult to distinguish residual disease from scar or normal tissue. When the evaluation of CR depends on this determination, 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. Subjects who continue on AMG 404 treatment, and/or other cancer therapies following confirmation of radiographic progressive disease will have radiological imaging assessment every 8 (± 1) weeks thereafter **following the confirmation of radiological progression** for Cohorts 1-9, [redacted].

If a subject discontinues treatment for reasons other than progression, tumor evaluations should continue according to the Schedule of Activities (Section 3.2) until progression or start of a new treatment regimen.

10.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (see Section 3.2).

10.2.3.1 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 13.5.

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

10.2.3.1.1.1 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 13.5

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of the safety follow-up period of 140 days [± 7 days] after last dose of IP are reported using the Event CRF.

[redacted]

10.2.3.1.1.2 Serious Adverse Events

For Cohorts 1-[redacted] the investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of the **safety follow-up period of 140 days (± 7 days) after last dose of IP** are reported using the Event CRF. [redacted].

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 13.5. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

Since the criteria **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 severity must be recorded in the subject medical records.**

10.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period

If the investigator becomes aware of serious adverse events **suspected to be related to investigational products after** the protocol-required reporting period (as defined in Section 10.2.3.1.1.2) **is complete, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event on the Events CRF.**

After End of Study, there is no requirement to actively monitor study subjects after the study **has ended with regards to study subjects treated by the investigator.** However, if the investigator becomes aware of serious adverse events **suspected to be related to investigational product, then these** serious adverse

events **will be r**eported 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.

10.2.3.1.2 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.

10.2.3.1.3 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 9.3). Further information on follow-up procedures is given in Section 13.5.

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.

10.2.3.1.4 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.

10.2.3.1.5 Safety Monitoring Plan

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

10.2.3.1.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male study subjects will be collected after the start of study treatment, and until 6 months for female study subjects and 8 months for female partners of male study subjects after the last dose of AMG 404.

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 13.6. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

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

Further details regarding pregnancy and lactation are provided in Section 13.6.

10.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure (BP), respiratory rate, heart rate and temperature. Subject must be in rested and calm state for at least 5 minutes before BP assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. Record all measurements on the vital signs eCRF.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs/temperature eCRF. Vital signs will be recorded by the investigator or designee at screening and time points specified in the Schedule of Activities (see Section 3.2).

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

10.2.3.3 Electrocardiograms (ECGs)

Subject must be in a 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 the most recumbent position as possible.

ECGs should be performed in accordance with the Schedule of Activities (see Section 3.2), in triplicate, in a standardized method, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

All ECGs will be triplicates with each tracing approximately 30 seconds apart and run consecutively.

For subjects enrolled to Cohorts 1, 2 and 4, triplicate ECGs must be performed at

- Screening
- Cycle 1: day 1 predose, end of infusion, and 4 hours postdose
- Cycle 2: day 1 end of infusion
- Cycle 3: day 1 end of infusion
- Cycle 4: day 1 end of infusion
- Cycle 5: day 1 end of infusion
- Beginning with Cycle 6, ECGs will be done if clinically indicated

For subjects enrolled to Cohort 3, and Cohorts **6-9** triplicate ECGs must be performed at screening and then as clinically indicated.

The PI or designated sub-investigator will review all ECGs. ECGs will be transferred electronically to a central Amgen vendor. Once reviewed and signed by PI or sub-investigator, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Standard ECG machines will be provided by Amgen for all study-related ECG requirements.

10.2.4 Clinical Laboratory Assessments

Refer to Section 13.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 3.2) for the timing and frequency. All tests (except for PK [redacted]) are to be performed at a local laboratory and test results are to be recorded in the eCRF. Additional safety laboratory assessments may be performed if clinically indicated at the discretion of the investigator.

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

All protocol-required laboratory assessments, as defined in Section 13.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 3.2).

10.2.4.1 Pregnancy Testing

A serum pregnancy test must be performed at screening and within 48 hours of cycle 1 dose of AMG 404; beginning with cycle 2, a urine or serum pregnancy test must be

performed within 48 hours prior to the AMG 404 dose for females of childbearing potential (see Schedule of Activities Section 3.2).

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

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 13-3). Refer to Section 13.6 for contraceptive requirements.

[redacted]

10.2.5 Pharmacokinetic Assessments

All subjects enrolled will have pharmacokinetic samples assessed.

Blood samples will be collected for measurement of serum concentrations of AMG 404 as specified in the Schedule of Activities (Section 3.2), [redacted] 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.

[redacted]

10.2.7 Antibody Testing Procedures

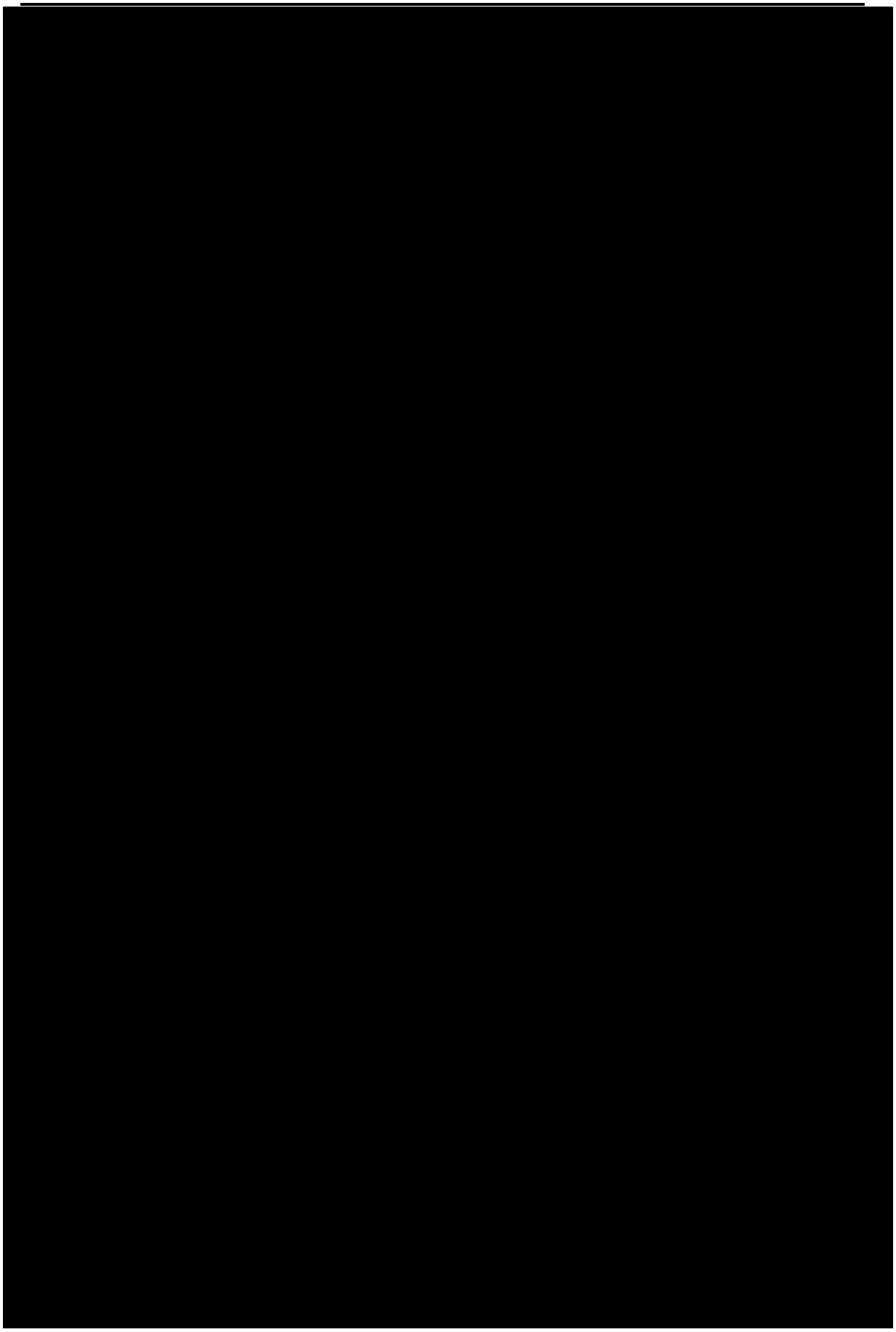
Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Section 3.2) for the measurement of anti-AMG 404 antibodies. [redacted]

Samples testing positive for binding antibodies to AMG 404 [redacted] may be further characterized. Additional blood samples may be obtained to rule out anti-AMG 404 [redacted] antibodies during the study.

Subjects who test positive for anti-AMG 404 [redacted] antibodies at the final scheduled antibody time point and have clinical sequelae that are considered potentially related to an anti-AMG 404 [redacted] antibody response will be asked to return for additional follow-up testing. Sample collection and testing will occur approximately every 3 months from the safety follow up visit until: (1) anti-AMG 404 [redacted] antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of AMG 404 [redacted] All follow-up results, both positive and negative, will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Refer to the Schedule of Activities (Section 3.2), as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions.

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

11. Statistical Considerations

11.1 Sample Size Determination

Up to 275 evaluable subjects will be enrolled in this study. Approximately, 2 to 4 DLT-evaluable subjects will be enrolled in Cohort 1. Approximately, 6 to 9 DLT-evaluable subjects will be enrolled each in Cohort 2. Approximately, 20 subjects will be enrolled each in Cohorts 3, 4, and 6 all outside of China. Approximately, 12 subjects will be enrolled to Cohort 5 in China/Taiwan/Hong Kong. Approximately, 40 subjects, respectively, will be enrolled to Cohort 7, Cohort 8, and Cohort 9. [redacted].

With 2 subjects in Cohort 1, there is a 36 – 55% probability of observing at least 1 DLT. With 4 subjects in Cohort 1, there is a 59 - 80% probability of observing at least 1 DLT if the true DLT rate is 20 – 33%.

Similarly, with 6 subjects per cohort, there is a 74 - 91% probability of observing at least 1 DLT. With 9 subjects per cohort, there is an 87 - 97% probability of observing at least 1 DLT if the true DLT rate is 20-33%.

In Cohorts 3, 4, 6, [redacted] a subject number of 20 will provide an 88% probability of observing at least one adverse event with 10% incident rate. An exact 80% binomial confidence interval (CI) will be provided for overall response rate. With the 20 subjects and 25% overall response rate, the expected 80% CI would be 13% to 42%.

In Cohort 5, a subject number of 12 will provide a 72% probability of observing at least one adverse event with 10% incident rate. An exact 80% binomial confidence interval (CI) will be provided for overall response rate. With the 12 subjects and 25% overall response rate, the expected 80% CI would be 10% to 48%.

In Cohort 7, Cohort 8, and Cohort 9, the sample size is N~40 subjects. A subject number of N~40 subjects will provide an 87% probability of observing at least one adverse event with 5% incident rate. An exact 80% binomial confidence interval (CI) will be provided for overall response rate. With the 40 subjects and 25% overall response rate, the expected 80% CI would be 16% to 36%.

[redacted]

11.2 Analysis Sets, [redacted] and Covariates

11.2.1 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 one dose of AMG 404.

The PK Analysis Set will contain all subjects who have received at least 1 dose of AMG 404 and have at least 1 PK sample collected. These subjects **may** be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

11.2.2 Covariates

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

[redacted]

[redacted]

11.3 Adaptive Design

Dose level decisions are based on a modified toxicity probability interval design (mTPI). The mTPI was developed by Ji et al. (2010). The mTPI models the probability of toxicity for each dose level using a Bayesian model where each dose level has the same prior on the probability of toxicity, a Beta (1,1). When subjects are treated at the current dose level, the posterior probability of toxicity is updated using the observed data from this level. Dose level recommendation are made based on this posterior probability of toxicity, using three toxicity probability intervals (TPI).

- Under-dosing TPI: DLT rate from 0 to < 20%
- Target TPI: DLT rate from 20% to 33%
- Over-dosing: DLT rate > 33%

For the current dose level and after adjusting for the width of the under-dosing TPI, if the DLT rate is most likely in the under-dosing TPI then the recommendation is to dose escalate. If the DLT rate is most likely in the target TPI then the recommendation is to stay at the current level. If the DLT rate is most likely in the over-dosing TPI then the recommendation is to stop the enrollment. If DLTs are observed, the maximum tolerated dose (MTD) is the dose level with a DLT toxicity rate closest to 26.7% (Ji et al. 2010).

During enrollment and treatment at the RP2D using data from cohorts 3 and 6 and additionally using data from cohorts 7-9, objective response rate will be monitored with futility stopping rules described in Section 11.4.1.1. These futility stopping rules are selected using practical considerations.

During enrollment and treatment at the RP2D using data from cohorts 3 and 6 and cohorts 7-9, subject incidence of grade 4 treatment related adverse events will be monitored with safety stopping rules described in Section 11.4.1.1. The safety stopping rules use a Bayesian approach proposed by Thall, Simon, and Estey (1995) to terminate a cohort if the posterior probability that the subject incidence of grade 4 or higher treatment-related adverse events is greater than 20% is > 80%. The stopping boundaries assume a prior distribution of Beta (0.40, 1.60).

11.4 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 6.3.1.

11.4.1 Planned Analyses

11.4.1.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. In the dose level review meetings, Amgen, in consultation with the site investigators, will review all available cumulative data by cohort prior to making dose determination decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all dose level review meetings and considered in all enrollment and dosing decisions.

Additional details regarding the dose review meeting are providing in Sections 8.4.1 and 13.3.

There is a planned treatment of N~40 subjects at the RP2D with enrollment to cohorts 3 and 6. Additionally, there is a planned treatment of N~40 subjects at the RP2D with enrollment to Cohort 7, N~40 subjects enrolled to Cohort 8 and N~40 subjects enrolled to Cohort 9. For each of these cohorts (Cohort 3/6, Cohort 7, Cohort 8, Cohort 9), futility will be assessed after treating 15 and 25 subjects for at least 3 months. If the observed rate of responses is consistent with a lower than 15% response rate, enrollment and treatment at the RP2D may be terminated due to futility. For purposes of assessing futility, a response is defined as an objective response per RECIST 1.1. The guidelines for early termination due to futility are as follows:

Number of Treated Subjects	Futility Termination Guideline
15	1 or fewer responders
25	4 or fewer responders
40	Enrollment to dose expansion cohort complete

If the true response rate is 15% then these termination guidelines result in a 69.4% probability of terminating dose expansion early with an expected sample size of 26.4 subjects. If the true response rate is 30% then there is a 90% probability of continuing enrollment to N~40 total subjects.

During this enrollment and treatment at the RP2D combining data from cohorts 3, 6, 7, 8 and 9 (up to 160 total subjects enrolled) [redacted], Amgen will conduct evaluations of the ongoing subject incidence grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible early termination of a cohort has been reached. If the threshold is met in the combined

monotherapy data of expansion cohorts 3, 6, 7, 8, and 9 enrollment to all ongoing cohorts in the study, [redacted], will be halted pending review of safety data by the DLRT. If the threshold is met in a specific cohort, then enrollment to the specific cohort will be halted pending review of safety data by the DLRT. After receiving the DLRT recommendation, Amgen will choose to take one of the following actions.

When overall safety threshold exceeded in combined monotherapy data of expansion cohorts 3, 6, 7, 8, and 9:

1) Terminate the trial
2) Amend the protocol to potentially improve the benefit/risk for subjects (eg, increase safety monitoring, modify dose/schedule, mandate premedication)
3) Continue monotherapy dose expansion cohorts and other cohorts, as appropriate, without any changes

When cohort-specific safety threshold exceeded:

1) Terminate enrollment to the cohort
2) Amend the protocol to potentially improve the benefit/risk for subjects in the cohort of concern (eg, increase safety monitoring, modify dose/schedule, mandate premedication)
3) Continue enrollment to the specific cohort (as appropriate) without any changes

The methods for deriving the stopping boundaries overall for the combined monotherapy data of expansion cohorts 3, 6, 7, 8 and 9, or for within a cohort are described in Section 11.3 with the stopping boundaries overall for the combined monotherapy data of expansion cohorts 3, 6, 7, 8 and 9 presented in Table 11-1 and stopping boundaries for within a cohort presented in Table 11-2. Operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in Table 11-3.

(Overall the combined monotherapy data of expansion cohorts 3, 6, 7, 8 and 9) and in Table 11-4 (cohort with planned sample size of 40 subjects). The operating characteristics in Table 11-3 and Table 11-4 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 11-1 and Table 11-2 are based on situations where the empirical evidence would result in a posterior probability of ≥ 80% that the true grade 4 or higher treatment-related adverse event rate is ≥ 20%.

Table 11-1. Stopping Boundary Overall for Combined Monotherapy Data of Cohorts 3, 6, 7, 8, and 9 with Posterior Probability of 80% and Grade 4 or Higher Treatment-Related Adverse Event Limit of 20%

Number of subjects	Stop study if observing this many subjects with grade 4 or higher treatment-related adverse events
10	≥ 4
20	≥ 6
30	≥ 9
40	≥ 11
50	≥ 13
60	≥ 15
70	≥ 18
80	≥ 20
90	≥ 22
100	≥ 24
110	≥ 26
120	≥ 28
130	≥ 31
140	≥ 33
150	≥ 35
160	Combined Monotherapy Data for Cohorts 3, 6, 7, 8 and 9 Complete

Table 11-2. Stopping Boundary for Enrollment within Cohorts 3, 6-[redacted] Individually with Posterior Probability of 80% and Subject Incidence of Grade 4 or Higher Treatment-Related Adverse Event Limit of 20%

Number of subjects treated	Stop cohort enrollment if observing this many subjects with grade 4 or higher treatment-related adverse events
5	≥ 3
10	≥ 4
20	≥ 6
30	≥ 9
40	Cohort Enrollment Complete*

* Enrollment for cohorts 7, 8, and 9 completes after n = 40 subjects enrolled. Enrollment for cohorts 3, 6, [redacted] completes after n = 20 subjects enrolled. [redacted]. Early stopping rules (eg, at 5 or 10 treated subjects) are the same regardless of planned maximum sample size in a cohort.

Table 11-3. Operating Characteristics with Batch Size of 10 Subjects (Combining All Monotherapy Data of Expansion Cohorts 3, 6, 7, 8 and 9)

True grade 4 or higher treatment-related adverse event rate	Probability of early stopping of dose expansion	Average sample size of overall combined monotherapy data
0.10	2.1 %	156.9
0.15	12.7 %	143.1
0.20	46.4 %	105.8
0.25	86.4 %	58.7
0.30	98.9 %	31.5

Table 11-4. Operating Characteristics With Batch Size of 10 Subjects (Cohort-Specific Enrollment with Maximum Cohort Sample Size of n=40 Subjects)

True grade 4 or higher treatment-related adverse event rate	**Probability of early stopping of cohort enrollment**	**Average cohort sample size**
0.10	**2.0 %**	**39.5**
0.15	**9.7 %**	**37.6**
0.20	**25.8 %**	**33.9**
0.25	**47.8 %**	**28.8**
0.30	**69.2 %**	**23.4**

11.4.1.2 Primary Analysis

The primary analysis will occur when target enrollment is complete, and each subject had the opportunity to complete 6 months on study or withdraws from study.

11.4.1.3 Final Analysis

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

11.4.2 Methods of Analyses

11.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamics [redacted] by **cohort, or** time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented. All descriptive statistics and graphical summaries may be presented separately for Cohort 5, [redacted] versus all the other cohorts. Similarly, all the efficacy analyses in Section 11.4.2.2 and all the safety analyses in Section 11.4.2.3 may be conducted separately for Cohort 5, [redacted] versus all the other cohorts. [redacted].

Efficacy endpoints will be summarized separately for Cohort 7, Cohort 8, Cohort 9, [redacted].

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

11.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	For all subjects treated at the RP2D and separately by cohort, the following analyses will be done. The proportion of subjects with an objective tumor

	response (partial and complete response) and disease control rate (DCR) (partial or complete control) with corresponding exact 80% CI will be calculated and tabulated. Similarly, the proportion of subjects and 80% CI will be tabulated for 1-year duration of overall response, 1-year PFS, 1-year duration of stable disease **and 1-year OS**. Kaplan-Meier curve will be presented for duration of overall response, PFS, **OS** and duration of stable disease with estimates for rate and 80% CI at selected weeks if data allows.
Exploratory	Not applicable

11.4.2.3 Safety Analyses

11.4.2.3.1 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 404. The statistical analysis methods are described in sections 11.4.2.3.2 through 11.4.2.3.6.

11.4.2.3.2 Adverse Events

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

11.4.2.3.3 Laboratory Test Results

Clinical chemistry, hematology, and urinalysis data will be **summarized**. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided.

11.4.2.3.4 Vital Signs

Depending on the size and scope of changes, summaries of vital signs data over time and/or changes from baseline over time may be provided.

11.4.2.3.5 Physical Measurements

The analyses of physical measurements **may** include summary statistics over time by treatment cohort.

11.4.2.3.6 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, QTcB) 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.

11.4.2.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 404 antibodies, [redacted], will be tabulated overall, and by **cohort**.

11.4.2.3.8 Exposure to Investigational Product

Details of AMG 404 administration will be **summarized**.

11.4.2.3.9 Exposure to Other Protocol-required Therapy

Not applicable.

11.4.2.3.10 Exposure to Concomitant Medication

All medication will be coded using the WHO drug dictionary. **All** concomitant medications will be **summarized**.

11.4.2.4 Other Analyses

The PK parameters of AMG 404 including, but not limited to, C_{max}, t_{max}, and AUC for serum AMG 404 will be estimated using non-compartmental methods for subjects where intense PK sampling was collected (ie, subjects in Cohorts 1-6 [redacted], at least 10 subjects in Cohorts 7-9). [redacted]. The parameter estimates will be 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 concentrations for AMG 404 [redacted] 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 404 exposure and efficacy/safety may be conducted.

[redacted]

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13. Appendices

13.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ADA	Anti-Drug Antibody
ADCC	Antibody-dependent cellular cytotoxicity
AML	Acute Myeloid Leukemia
AUC	area under the serum concentration-time curve
CFR	U.S. Code of Federal Regulations
CI	Confidence Interval
C_{max}	maximum observed serum concentration
CRF	case report form
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
ECL	Electrochemiluminiscent
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
Enrollment	Date of enrollment confirmation letter from Amgen
EOT	End of Treatment
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 [redacted] pharmacodynamic (PD) 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

Abbreviation or Term	Definition/Explanation
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
FIH	First in Human
FSH	follicle stimulating hormone
FFPE	Formalin fixed paraffin embedded
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone replacement therapy
HUVEC	Human Endothelial Cells
IBG	Independent Biostatistics Group
ICF	informed consent form
ICH	International Conference on Harmonisation
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IP	**investigational product**
IPIM	Investigational Product Instruction Manual
IPRO	Immunophenotyping receptor occupancy
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	Intravenous
LLOQ	Lower limit of quantification
(m)TPI	(modified) Toxicity Probability Interval
ORR	Overall Response Rate
PBL	Peripheral blood leukocytes
PFS	Progression free survival
PPP	Platelet poor plasma
SAT	safety assessment team

Abbreviation or Term	Definition/Explanation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product administered to the subject
TBL	total bilirubin
t_{max}	time to achieve C_{max}
SUSAR	suspected unexpected serious adverse reaction
TMF	trial master file
ULN	upper limit of normal

13.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 13-1 will be performed by the local laboratory (unless specified otherwise).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 7.1 and 7.2 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 13-1. Analyte Listing

Local Laboratory: Chemistry	Local Laboratory: Coagulation	Local Laboratory: Urinalysis	Local Laboratory: Hematology	Other Labs
Sodium Potassium Chloride Bicarbonate or CO_2 Total protein Albumin Calcium Calcium Corrected Glucose BUN or Urea/Total Urea Creatinine Estimated CrCl GFR, MDRD calculation Total bilirubin ALP AST (SGOT) ALT (SGPT) TSH Free T4	APTT PT/INR	Specific gravity pH Blood Protein Glucose Bilirubin WBC RBC Epithelial cells Bacteria Casts Crystals	RBC Hemoglobin Hematocrit MCV Platelets WBC Differential • Total Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Central Laboratory: Antibodies PK sampling Whole blood for cytometry Serum[2] [redacted] PD-L1 dMMR MSI [redacted] Local Laboratory: Serum or Urine Pregnancy Hep B surface antigen Hep B core antibody Hep C antibody HIV ACTH ANA ANCA (cytoplasmic and perinuclear) PD-L1 dMMR MSI [redacted]

[redacted]

[2] Not applicable to China

ACTH = Adrenocorticotropic hormone; ANA = Antinuclear Antibodies; ANCA = Antineutrophil cytoplasmic antibodies; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; dMMR = Mismatch Repair Deficiency; [redacted] HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MSI = Microsatellite Instability; PD-L1 = Programmed Death Ligand 1; PK = pharmacokinetics; PT = prothrombin time; APTT = partial thromboplastin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell count

13.3 Appendix 3. Study Governance Considerations

Committee(s)

Dose Level Review Team

Dose level review team (DLRT) meetings will be held to review data, monitor safety, and make recommendations on dose determination. See Section 8.4.1 for detailed information on the DLRM and DLRT.

Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen

- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

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

Informed Consent Process

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

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

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

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

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

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject [or a legally acceptable representative] and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 9.

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

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

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

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

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate

signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

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

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

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

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

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

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

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

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does

not guarantee authorship. The criteria described below are to be met for every publication.

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

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

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

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

Source Documents

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

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the 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.

13.4 Appendix 4. Toxicity Management Guidelines

Table 13-2. 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 one lobe of the lung of 25-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider additional immunosuppressive agent (eg, infliximab, mycophenolate, cyclophosphamide) if refractory to corticosteroids.	Monitor subjects for signs and symptoms of pneumonitis. Evaluate subjects with suspected pneumonitis with radiographic imaging. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 (severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated)	Permanently discontinue		
	Grade 4 (life-threatening respiratory compromise, urgent intervention indicated [intubation])			

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Table 13-2. 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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Table 13-2. 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**[1]	Grade 1 (AST or ALT< 3 x ULN) without elevated total bilirubin	Continue	Consider holding for concerning lab value trend.	Monitor with liver function tests more frequently until returned to baseline or stable. Additional management per institutional and professional society guidelines.
	Grade 2 (AST or ALT 3-5 x ULN) without elevated total bilirubin	Withhold	Consider corticosteroids at an initial dose of 0.5 to 1 mg/kg/d prednisone (or equivalent) followed by taper.	
	Grade 3 (AST or ALT 5-20 x ULN) without elevated total bilirubin [Without a clear alternative etiology. If a clear alternative etiology, then withhold, do not discontinue AMG 404.]	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 (AST or ALT > 20 x ULN) without elevated total bilirubin [Without a clear alternative etiology. If a clear alternative etiology, then withhold, do not discontinue AMG 404.]		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.	
	Grade > 1 (AST or ALT > 3 x ULN) with total bilirubin > 1.5 x ULN [Without a clear alternative etiology. If a clear alternative etiology, then withhold, do not discontinue Consider holding for concerning lab value trend. AMG 404.]		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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Table 13-2. 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 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Administer corticosteroids at an initial dose of 1 mg/kg/d prednisone (or equivalent) followed by taper. In addition, initiate hormonal replacement therapy as clinically indicated.	Monitor for signs and symptoms of hypophysitis. Consider endocrine consultation.
Adrenal Insufficiency	Grade 3 or 4 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Initiate IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg [if the diagnosis is not clear and ACTH stimulation testing will be needed]). Taper stress-dose corticosteroids down to maintenance doses (prednisone 5 to 10 mg daily) over 1-2 weeks after discharge.	Monitor for signs and symptoms of adrenal insufficiency. Consider endocrine consultation.
Hypothyroidism	Grade 3 or 4 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Initiate thyroid hormone supplementation.	Monitor subjects for signs and symptoms of hypothyroidism. Consider endocrine consultation.
Hyperthyroidism	Grade 3 or 4 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Initiate β-Blocker (eg, atenolol, propranolol) for symptomatic relief. For severe symptoms or concern for thyroid storm, initiate prednisone 1-2 mg/kg/d (or equivalent) tapered over 1-2 weeks. Consider use of SSKI or thionamide (methimazole or PTU).	Monitor subjects for signs and symptoms of hyperthyroidism. Consider endocrine consultation.

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Table 13-2. 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 hyperglycemia (> 250 to 500 mg/dL [> 13.9 to 27.8 mmol/L])	Withhold	Initiate insulin therapy.	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes. Consider endocrine consultation.
	Grade 4 hyperglycemia (> 500 mg/dL [> 27.8 mmol/L])			
Nephritis and Renal Dysfunction	Grade 2 (serum creatinine >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN)	Withhold	Administer corticosteroids at an initial dose of 0.5 to 1 mg/kg/d prednisone (or equivalent) followed by taper. If worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/d prednisone (or equivalent).	Monitor changes in renal function. Evaluate for other causes of renal dysfunction (eg, recent IV contrast, medications, fluid status, etc)
	Grade 3 (serum creatinine >3.0 x baseline; >3.0 - 6.0 x ULN)	Permanently discontinue	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper.	
	Grade 4 (serum creatinine > 6 x ULN; dialysis indicated)			

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Table 13-2. 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	Grade 2 (moderate symptoms, some interference with ADL)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results obtained and negative for aseptic meningitis.	Monitor subjects for neurologic symptoms and exclude other etiologies (eg, infectious). Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.
	Grade 3 or 4 (severe symptoms, limiting self-care and aids warranted)	Permanently discontinue		

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Table 13-2. 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 [redacted] 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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Table 13-2. 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.

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

***Immune mediated hepatitis guidance adapted from the National Comprehensive Cancer Network (NCCN) Version 1.2020, Management of Immune Checkpoint Inhibitor-Related Toxicities*

[1] In addition to Table 13-2, which includes guidance on mitigation/management of suspected immune-mediated hepatitis, the protocol contains Table 12-4 in Appendix 8, which offers general mitigation guidance for potential Drug-Induced Liver Injury (DILI). When applicable, first refer to Table 13-2 for managing AST and/or ALT and/or total bilirubin elevations, when other liver parameters remain within normal limits (ie INR, ALP). Table 13-2, withholding and discontinuation guidance is more conservative than Table 12-4 guidance.

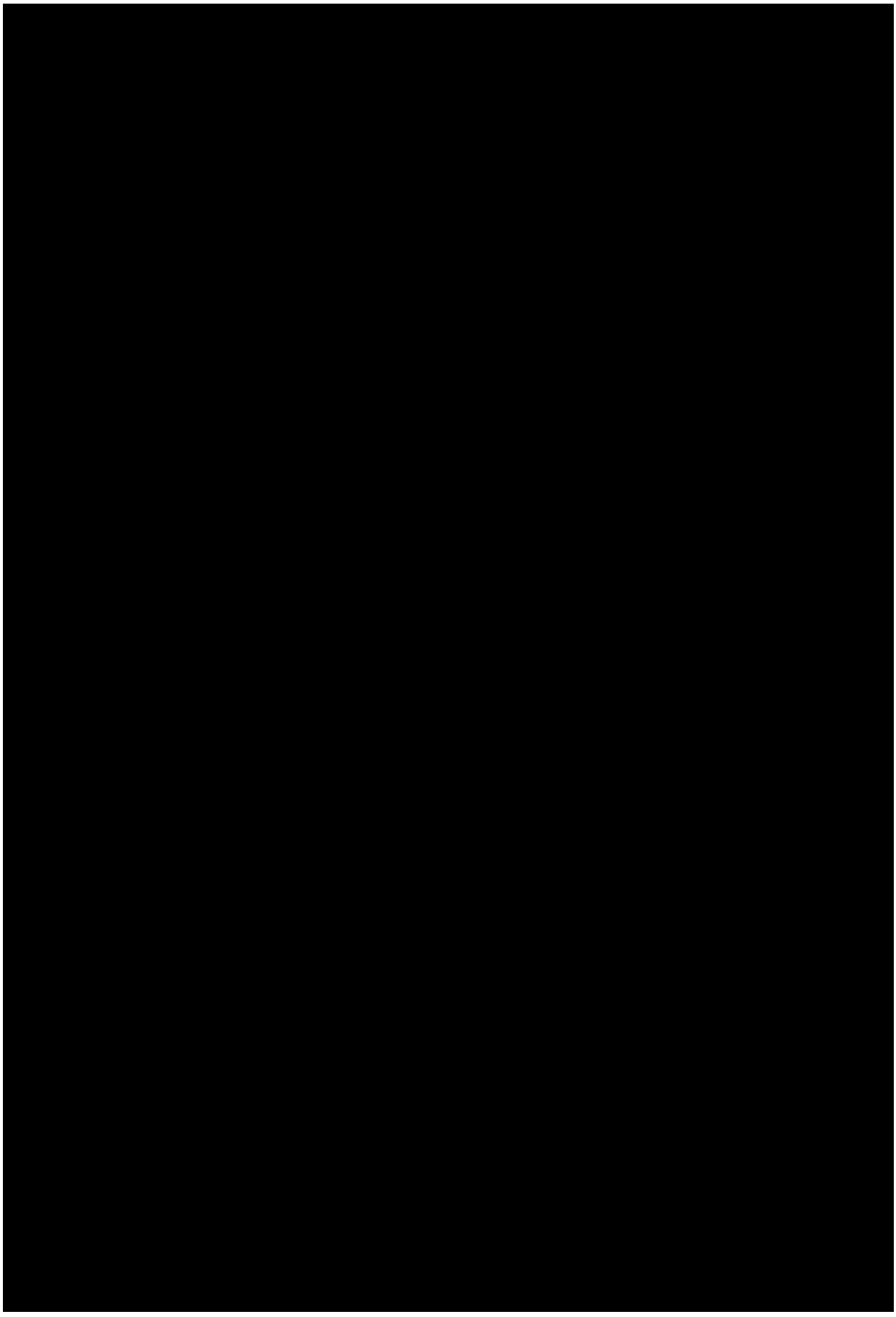


Table 13-5. Management of Infusion-Related Reactions With AMG 404

Severity (CTCAE Grade Version 5.0)	AMG 404 Dose Modification	Management	Premedication at Subsequent Dosing
Grade 1 (mild transient reaction; infusion interruption not indicated; intervention not indicated)	Interrupt 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 or slow the rate of the infusion to 50 % or less of the standard rate. For subjects who develop grade 2 infusion-related reaction despite adequate premedication, permanently discontinue AMG 404.	• 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 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

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

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment emergent adverse event 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 the underlying disease under study (ie, advanced solid tumor) 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, non-small cell lung cancer, malignant melanoma, etc). 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: o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); o Dates of onset and resolution (if resolved); o Did the event start prior to first dose of investigational product, other protocol-required therapies; o Assessment of seriousness; o Severity (or toxicity defined below); o Assessment of relatedness to investigational product(s), non-investigational product(s), other protocol-required therapies, and/or study-mandated activity and/or procedures; o Action taken; and o Outcome of event. • If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event CRF • It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event CRF page. • If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The Common Terminology Criteria for Adverse Events, version 5.0 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product **non-investigational product(s), other protocol-required therapies**, and/or study-mandated **activity and/or** procedure and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure 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 as defined in Section 10.2.3.1.1, 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 paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event (eSAE) Contingency Report Form) (see Figure 13-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper-based Serious Adverse Event Contingency Report Form. • Once the study has ended, serious adverse event(s) should be reported to Amgen (regardless of causality) 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 13-1. Sample Electronic Serious Adverse Event Contingency Report Form (Paper-Based Form)

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

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

General Instructions

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

Types of Events to be reported on this form

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

1. **Site Information**

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

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

2. **Subject Information**

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

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

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

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

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –

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

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

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

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

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

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

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

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

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

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

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

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

4. **Hospitalization**

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

FORM-056000 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

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

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

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

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

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

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

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

A
Study # 20180143
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? AMG 404 No✓ / Yes✓	bevacizumab (MVASI) No✓ / Yes✓	<Fldevice> No✓ / Yes✓	<Fldevice> No✓ / Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 404	☐blinded ☒ open label							Lot #_____ ☐ Unknown Serial #_____ ☐ Unavailable / Unknown
bevacizumab (MVASI)	☐blinded ☒ open label							Lot #_____ ☐ Unknown Serial #_____

A Study # 20180143 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:

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

A Study # 20180143 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 - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

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

Study-specific contraception requirements for male and female of childbearing potential are outlined in Section 7.2.

Male and female study subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 6 months (female study subjects) and 8 months (male study subjects) after the last dose of AMG 404.

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 last dose of AMG 404, [redacted]
- Information will be recorded on the Pregnancy Notification Form (see Figure 13-3). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 6 months after last dose of AMG 404, [redacted] 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 13.5. 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 9.1 for details).

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, [redacted] and/or 8 months after last dose of AMG 404 the information will be recorded on the Pregnancy Notification Form. The form (see Figure 13-3) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 6 months after the last dose of AMG 404, [redacted]
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 221.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 6 months after discontinuing protocol-required therapies.

Figure 13-3. Pregnancy and Lactation Notification Forms

AMGEN Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20180143

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

If yes, provide date of delivery: mm_____/ dd_____/ yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

AMGEN Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20180143

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

13.7 Appendix 7. Sample Storage and Destruction

Any blood, [redacted], PK, and [redacted] sample collected according to the Schedule of Activities (Section 3.2) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand advanced solid tumors, the dose response and/or prediction of response to AMG 404, 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 [redacted] are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood, serum [redacted] 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 13.3 for subject confidentiality.

13.8 Appendix 8. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

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

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

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

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

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomyolosis, 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 13-6. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 1 week > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

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

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

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

If signs or symptoms recur with rechallenge, then Amgen investigational product is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 13-6) 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 13.5.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 13-6 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

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

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

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

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

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

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

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

13.9 Appendix 9. ECOG Performance Status and NYHA Classification

- Eastern Cooperative Oncology Group Performance Scale

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

Source: Oken et al, 1982

New York Heart Association Functional Classification

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

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

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

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

13.10 Appendix 10. Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (Modified RECIST 1.1)

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

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

Definitions

- **Measurable lesions:**
    - Measurable Tumor Lesions – Non-nodal lesions with clear borders that can be accurately measured in at least 1 dimension with longest diameter ≥ 10 mm in CT/MRI scan with slice thickness no greater than 5 mm. When slice thickness is greater than 5 mm, the minimum size of measurable lesion should be twice the slice thickness.
    - Nodal Lesions - Lymph nodes are to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI (scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
        - Nodal size is normally reported as two dimensions in the axial plane. The smaller of these measures is the short axis (perpendicular to the longest axis).
    - Irradiated Lesions - Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not measurable unless there has been demonstrated progression in the lesion prior to enrollment.
- **Non-measurable Lesions**
    - All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm but to < 15 mm short axis with CT scan slice thickness no greater than 5 mm) are considered non-measurable and characterized as non-target lesions.
    - Other examples of non-measurable lesions include:
        - Lesions with prior local treatment: tumor lesions situated in a previously irradiated area, or an area subject to other loco-regional therapy, should not be considered measurable unless there has been demonstrated progression in the lesion.
        - Biopsied lesions
        - Categorically, clusters of small lesions, bone lesions, inflammatory breast disease, and leptomeningeal disease are non-measurable.

Methods of Measurement

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

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

- **Target Lesions** - All measurable lesions up to a maximum of five (5) lesions per organ and ten (10) lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
  - Target lesions should be selected on the basis of their size (lesions with the longest diameter) and suitability for accurate repeated measurements.
  - Pathologic lymph nodes (with short axis ≥ 15 mm) may be identified as target lesions. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions.
  - A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference by which to characterize objective tumor response.
  - **Non-Target Lesions** - All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required**,** and these lesions should be followed as "present", "absent", or "unequivocal progression" throughout the study. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

Evaluation of Target Lesions

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

Evaluation of Non-target Lesions

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

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

Evaluation of Overall Response

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

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

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

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

NE = Not evaluable

Time Point Response: Subjects with Non-Target Disease Only

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

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

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

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

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

Special Notes on Response Assessment

- Nodal lesions – Lymph nodes identified as target lesions should always have the actual short axis measurement recorded, even if the nodes regress to below 10 mm on study. In order to qualify for CR, each node must achieve a short axis $<$ 10 mm, NOT total disappearance. Nodal target lesion short axis measurements are added together with target lesion' longest diameter measurements to create the sum of target lesion diameters for a particular assessment (time point).
- 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, it is recommended that the residual lesion be further investigated by fluorodeoxyglucose-positron emission tomography (FDG-PET) or PET/computed tomography (PET/CT), or possibly fine needle aspirate/biopsy, to confirm the CR status.

Confirmation Measurement / Duration of Response

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

Amendment 6

Protocol Title: A Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 404, a Programmed Death-1 (PD-1) Antibody, [redacted] in Patients With Advanced Solid Tumors

Amgen Protocol Number AMG 404 20180143

EudraCT Number: 2018-004268-80

NCT Number: NCT3853109

Amendment Date: 20 May 2022

Rationale:

The protocol, dated May 20th, 2022, was amended to discontinue clinical trial activities for study 20180143, to allow for extended treatment for an additional 24 months for subjects who continue to receive clinical benefit from treatment with AMG 404, to update safety language, and to clarify/correct other items in the protocol. Please note, the study is not being stopped for safety reasons or lack of efficacy.

Changes include:

- Updated Section 3.2 Schedule of Activities to include extended treatment for Cohorts 1-9.
- Updated Section 2 Protocol Synopsis and Section 3.1 Study Schema to clarify that Cohort 5 was a China/Taiwan/Hong Kong-specific expansion cohort
- Updated Section 4.5.3 Risks with current safety information.

[redacted]

- Deleted Section 7.2 Exclusion Criteria, exclusion criterion #242 to remove a duplicated criterion.

- Added Section 10.1.3 Extended Treatment Period for subjects who continue to receive clinical benefit from treatment with AMG 404 beyond 24 months of treatment.
- Updated Section 10.2.2 Efficacy Assessments to incorporate extended treatment and cohort closures.
- Updated Section 10.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period to clarify SAE collection post study.
- Updated safety template language.

[redacted]

- Administration, typographical, and formatting changes were made throughout the protocol.

Amendment 5

Protocol Titile: A Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 404, a Programmed Death-1 (PD-1) Antibody, [redacted] in Patients With Advanced Solid Tumors

Amgen Protocol Number (AMG 404) 20180143

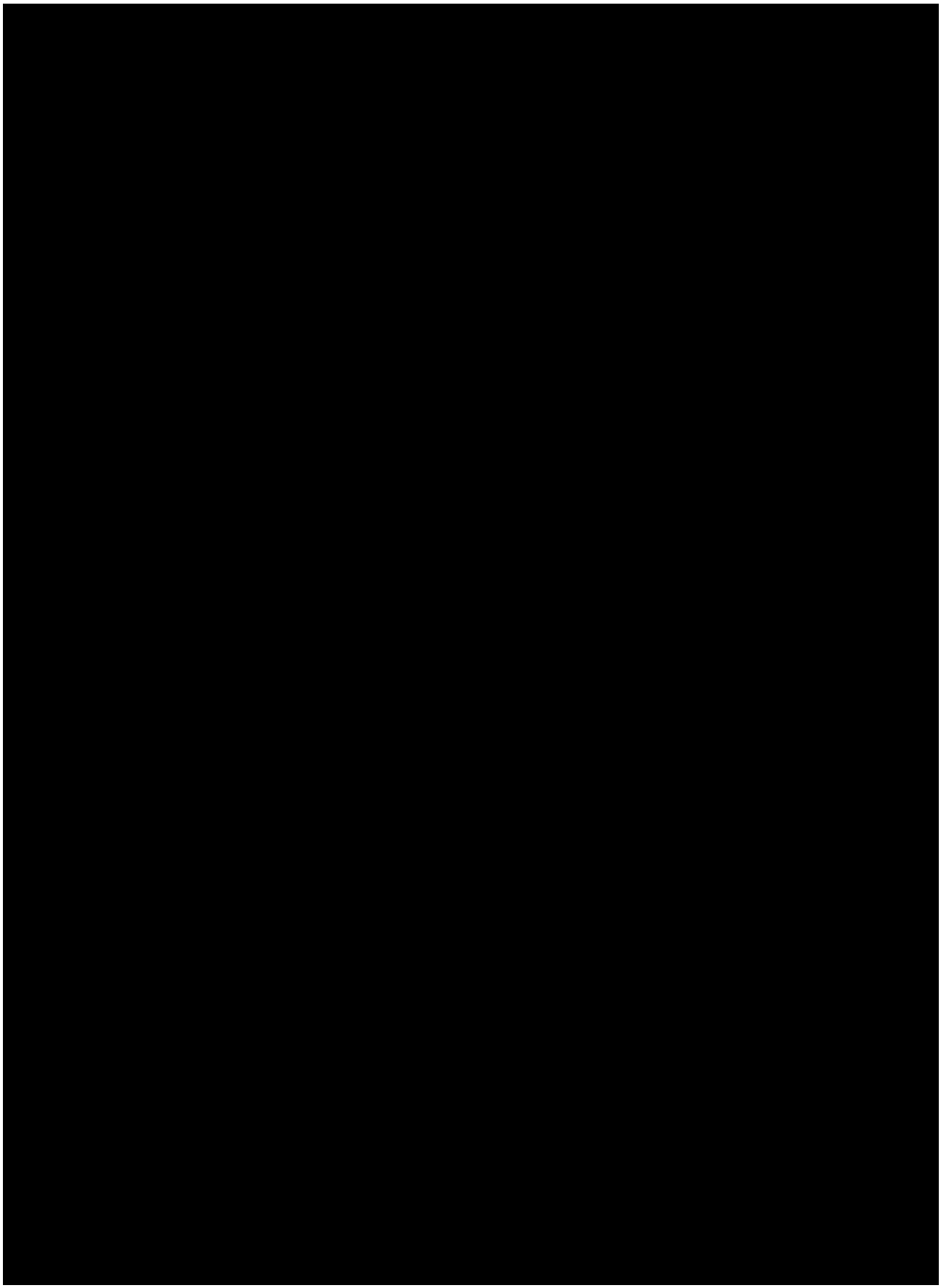
EudraCT Number: 2018-004268-80

Amendment Date: 16 July 2021

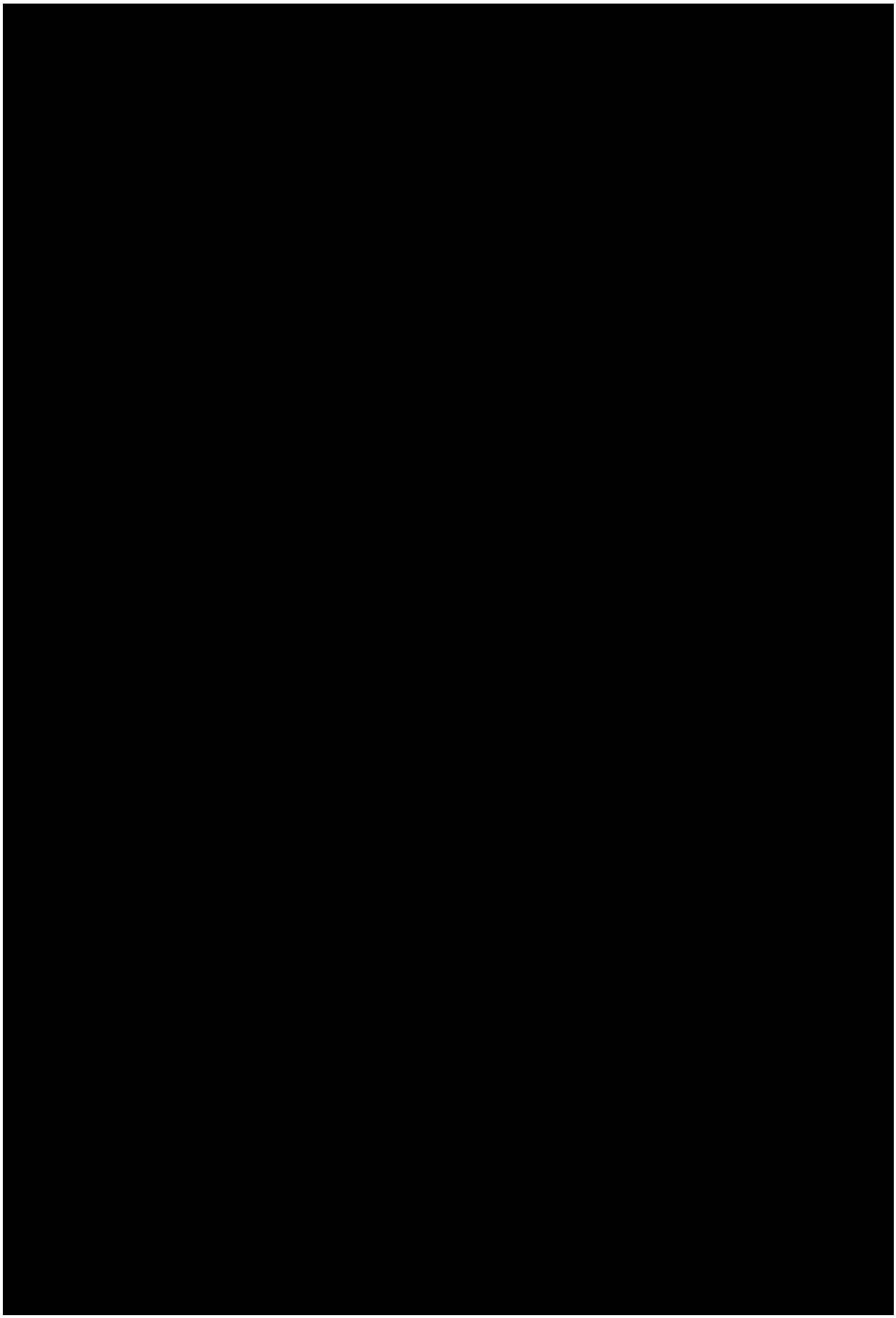
Rationale:

The following changes were made to the protocol, dated July 16th, 2021, [redacted] to expand cohort 5 to include additional NMPA certified sites for expanded access to subjects, to provide SARS-COV2 guidance to investigators and site staff, to update the AMG 404 stopping rules, and to clarify/correct other items in the protocol.

[redacted]



[redacted]



Cohort 5 changes include:

- Updated overall design (section 6.1) to include NMPA certified sites.
- Updated inclusion criterion #111 (section 7.1) to include NMPA certified sites.

SARS-COV2 changes include:

- Added dose modification guidelines (section 8.4.5) for SARS-COV2 infection.
- Added SARS-COV2 Vaccination guidance (section 8.8.2.1) for all Cohorts.

Other changes include:

- Updated and added stopping rules for AMG 404 monotherapy (section 11.4.1).
- Updated references (section 12).
- Updated template safety language.
- Administration, typographical and formatting changes were made throughout the protocol.

Description of changes:

Section: Global

Change: The Amgen global version date was changed from 24 November 2020 to **16 July 2021.**

Section: Global

Replace:

A Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 404,a Programmed Death-1 (PD-1) Antibody, in Patients With Advanced Solid Tumors

With:

A Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 404, a Programmed Death-1 (PD-1) Antibody, [redacted] in Patients With Advanced Solid Tumors

Section: Global

Replace: Table 2-1

With: **Section 3.2**

Section: Title Page, Key Sponsor Contact

Replace:

	Name:	[redacted], MD [redacted], DSc, MSc

Amendment 4

Protocol Title: A Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 404, a Programmed Death-1 (PD-1) Antibody, in Patients with Advanced Solid Tumors

Amgen Protocol Number (AMG 404) 20180143

Amendment Date: 24 November 2020

Rationale:

The following changes were made to the protocol, dated November 24th, 2020, to integrate revised contraceptive and safety follow-up requirements based on current half-life data, and to clarify/correct other items in the protocol.

Revised requirements based on current half-life data included:

- Updated exclusion criterion #221, 222, and 223 to clarify the time period for female and male restrictions regarding pregnancy and contraception.
- Updated section 7.4.3.4, section 9.2.3.1.6, and appendix 6 to clarify the time period for female and male restrictions regarding pregnancy and contraception.

Other changes include:

- Updated overall design to clarify subjects with complete response treatment duration beyond 12 months.
- Updated subject eligibility criteria to clarify prior systemic treatments excluded.
- Updated study schema formatting.
- Updated schedule of activities to reflect protocol updates.
- Updated risks in section 3.3.3 to include hypothyroidism.

[redacted]

- Updated exclusion criterion #201 to clarify benign asymptomatic tumor exception.
- Updated exclusion criterion #202 to clarify the exception of other malignancies which do not require systemic therapy.

- Updated exclusion criterion #208 to clarify corticosteroid exception.
- Updated exclusion criterion #217 to clarify anti arrhythmia medication.
- Updated language for AMG 404 interruptions or discontinuations due to safety reasons.
- Added dose modification due to surgery during study treatment clarification in section 7.4.5.
- Updated section 9.1.3, section 9.2.3.1.1.1, and section 9.2.3.1.1.2 to align with current safety language and requirements.
- Updated section 9.1.5 end of study to clarify end of study for a particular study subject.
- Updated section 9.2.2 efficacy assessments to clarify complete response evaluations.
- Updated Table 12-3 to clarify instructions for AMG 404 dose modification and management of toxicities.
- Updated section 9.2.8.5, section 9.2.8.5.1, section 10.4.2.4 to clarify pharmacokinetic [redacted] collections.
- Administration, typographical and formatting changes were made throughout the protocol

Amendment 3

Protocol Title: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 404, a Programmed Death-1 (PD-1) Antibody, in Patients With Advanced Solid Tumors

Amgen Protocol Number 20180143

IND Number 140964

EudraCT number 2018-004268-80

Amendment Date: 31 January 2020

Rationale:

The purpose of this amendment includes:

- To add Cohorts 7-9 to evaluate efficacy of AMG 404;
- To add additional subjects are being added to Cohort 4 to gain additional safety information at the higher dose;
- To revise the purpose, eligibility, statistics and tumor evaluation sections to align with the additional cohorts;
- [redacted]
- To add information on the Recommended Phase 2 Dose selection;
- To incorporate China Country Specific Supplement version 1 information; and
- To revise the hepatitis toxicity management (Appendix 4) to align with the hepatotoxicity stopping rules (Appendix 8).

In addition, grammatical and typographical errors were corrected throughout the protocol document.

The consent and addendum consent forms were revised to reflect protocol updates.

The version number and date on all documents was updated

Amendment 2

Protocol Title: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 404, a Programmed Death-1 (PD-1) Antibody, in Patients with Advanced Solid Tumors

Amgen Protocol Number 20180143

IND Number 140964

EudraCT number 2018-004268-80

Amendment Date: 15 July 2019

Rationale:

This purpose of this amendment is to:

- Add Cohort 5, a China specific cohort at the RP2D and added Inclusion Criteria 111 to define subject population for Cohort 5
- Add Cohort 6, additional subjects at the RP2D
- Revised Inclusion Criteria 109, decreasing eGFR for subjects enrolled to Cohorts 3 and 6 based on initial FDA feedback
- Dose-limiting toxicity (DLT) section updated based on Japanese Health Authority feedback
- Removal of Disease Related Events (DRE) to align with Amgen's internal guidelines

[redacted]

- Minor revisions/clarifications throughout

The consent and addendum consent forms were revised to reflect protocol updates.

The version number and date on all documents was updated

Amendment 1

Protocol Title: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 404, a Programmed Death-1 (PD-1) Antibody, in Patients with Advanced Solid Tumors

Amgen Protocol Number 20180143

IND Number 140964

EudraCT number 2018-004268-80

Amendment Date: 02 JAN 2019

Rationale:
This amendment reflects revisions in response to FDA feedback. The consent form was revised to reflect protocol updates and an addendum consent was added in response to FDA feedback.

The version date on all documents was updated and minor typos were corrected.

Protocol Revisions:

Section: Global
Replace:
The version is updated to Amendment **1** and the date is updated to **02 JAN 2019**.

Section: 1.0 Protocol Synopsis and Section 4.1
Replace: Delete strikethrough text, add bolded text

Overall Design
This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of AMG 404 in subjects with advanced solid tumors. The study may be conducted in Australia, United States, France, Poland, United Kingdom, Belgium, South Korea, Taiwan, Japan, and Canada. Other countries or regions may participate. The study will comprise of ~~3~~ **4** cohorts to evaluate the safety, tolerability, PK and PD of AMG 404 with the following doses: Cohort 1 – **240 mg Cohort 2-** 480 mg, Cohort ~~2~~3 – Expansion at the dose of 480 mg, and Cohort ~~3~~**4** – Exploratory Dose of 1050 mg. AMG 404 will be administered intravenously (IV) over approximately 30 minutes, every 4 weeks in subjects with advanced solid tumors. Cohorts ~~2~~**3** and ~~3~~**4** can be opened once Cohort ~~1~~**2** has been completed and determined to be tolerable. The DLT evaluation period will be 28 days. The Dose Level Review Meeting (DLRM) may recommend escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), continuation or delay in dosing, repetition or expansion of a cohort, de-escalation to a lower dose, or termination of the study. Administration of AMG 404 (in all cohorts) 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