Title Page

Protocol Title:		A Phase 1b Multicenter, Open-label, Expansion Study to Assess the Safety and Efficacy of AMG 420 in Subjects With Relapsed and/or Refractory Multiple Myeloma
Short Protocol Title:		A Phase 1b Study to Assess AMG 420 in Subjects with Relapsed and/or Refractory Multiple Myeloma
Protocol Number:		20160370
Investigational Product:		AMG 420
Trade Name		Not applicable
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EudraCT Number:		2018-002879-17
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Version/Date:		**Data Element Standards Version** 6.1

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

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Investigator's Agreement:

I have read the attached protocol amendment entitled A Phase 1b Multicenter, Open-label, Expansion Study to Assess the Safety and Efficacy of AMG 420 in Subjects With Relapsed and/or Refractory Multiple Myeloma,dated **17 September 2021**, and agree to abide by all provisions set forth therein.

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

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

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

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: A Phase 1b Multicenter, Open-label, Expansion Study to Assess the Safety and Efficacy of AMG 420 in Subjects With Relapsed and/or Refractory Multiple Myeloma

Short Protocol Title: A Phase 1b Study to Assess AMG 420 in Subjects with Relapsed and/or Refractory Multiple Myeloma

Study Phase: 1b

Indication: Relapsed and/or Refractory Multiple Myeloma

Rationale

Patients who have relapsed and/or refractory multiple myeloma (RRMM) and are refractory to proteasome inhibitors (PIs) and immunomodulatory drugs experience poor prognosis despite recent advances in treatment. AMG 420 is being developed as another treatment option by targeting the B-cell maturation antigen (BCMA, TNFRSF17, CD269) because of its function in promoting plasma cell survival, highly restricted expression in cells of the B-cell lineage, and elevated expression in malignant plasma cells. This study will further establish the safety and tolerability, as well as evaluate the efficacy, of AMG 420.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Phase 1b	
Primary	
• Establish the safety and tolerability of AMG 420 at dose levels of 400 μg/day and 600 μg/day in subjects with relapsed and/or refractory multiple myeloma (RRMM)	• Dose-limiting toxicities (DLTs), treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
Key Secondary	
• Estimate overall response rate (ORR) and duration of response (DOR) of AMG 420 in subjects with RRMM	• ORR • DOR
• Evaluate the rate of minimal residual disease (MRD)-negativity at the time of CR	• MRD negativity at the time of CR

Objectives	Endpoints
Secondary	
• Establish the safety and tolerability of AMG 420 in subjects with extramedullary relapsed multiple myeloma	• DLTs, treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, ECGs, and clinical laboratory tests
• Characterize the pharmacokinetics (PK) of AMG 420 when administered as 4-week continuous intravenous (cIV) infusion	• AMG 420 PK parameters including, but not limited to, half-life ($t_{1/2}$), clearance, and apparent C_{ss}
• Evaluate other measures of anti-myeloma activity of AMG 420 in subjects with RRMM: – Time to response – Progression-free survival (PFS) – Overall survival (OS) – Best overall response (BOR)	• Efficacy parameters according to International Myeloma Working Group (IMWG) response criteria, per investigator assessment: – Time to response – PFS – OS – BOR

Hypotheses

A safe and tolerable dose of AMG 420 will have evidence of anti-tumor activity in patients with RRMM as measured by the rate of overall response.

The overall response rate (ORR) according to International Myeloma Working Group (IMWG) response criteria along with 95% CI will be calculated per investigator assessment for subjects with RRMM. The lower bound of the binomial 2-sided 95% confidence interval for ORR not lower than 35% is considered clinically meaningful.

Overall Design

This is a phase 1b, multicenter, non-randomized, open-label expansion study. AMG 420 will be evaluated in adult subjects with RRMM.

The study will consist of up to a 21-day screening, a treatment period, safety follow-up (SFU), and long-term follow-up (LTFU) period. In the treatment period, treatment will be continued until progressive disease (PD) or relapse as defined by IMWG response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation. All subjects will be assessed for anti-myeloma activity according to the IMWG response criteria. An SFU visit will be conducted 30 (+3) days after last administration of AMG 420, and an LTFU period that will begin after the SFU visit is completed. The total duration of the LTFU will be up to

5 years from the first dose of AMG 420, or until subject death, whichever is first (See Study Schema).

Phase 1b (Monotherapy Dose Confirmation)

In phase 1b, approximately 10 subjects will be treated at the 400 μg/day dose (comprising cohort 1). Approximately 10 subjects will be treated at the 600 μg/day dose level (cohort 2).

The dose level review team (DLRT) will convene and review all available safety, laboratory, and pharmacokinetic (PK) data at the following scheduled time points:

- After at least 10 subjects in phase 1b cohort 1 (400 μg/day dose level) have had the opportunity to complete the 4-week infusion period of the first treatment cycle: On the basis of this review, the DLRT will make a recommendation regarding the initiation of phase 1b cohort 2 (600 μg/day dose level).
- After at least 3 subjects with extramedullary (EM) relapsed disease in phase 1b cohort 1 (400 μg/day dose level) have had the opportunity to complete the 4-week infusion period of the first treatment cycle: On the basis of this review, the DLRT will make a recommendation regarding the appropriateness of continued enrollment of subjects with EM relapsed disease in phase 1b cohort 2 (600 μg/day dose level). Please note that enrollment of subjects with EM relapsed disease in phase 1b cohort 2 will not be allowed until this safety review of the first 3 subjects with EM disease is completed by the DLRT.
- After the first 3 subjects have been dosed with AMG 420 at 600 μg/day for the full 4-week infusion cycle in phase 1b cohort 2.

The safety data will be reviewed on an ongoing basis and enrollment may be terminated at any time. To further reduce the risk of overdose to ongoing and future subjects, protocol-defined enrollment holding rules will be used. These rules are based on a modified Toxicity Probability Interval (mTPI) (Ji et al, 2010), where the target Toxicity Probability Interval (TPI) is a dose-limiting toxicity (DLT) probability from 20% to 33% and the overdose TPI is > 33% DLT probability. Enrollment to the ongoing dose level/schedule will be paused per the following rules during enrollment into phase 1b cohort 1 and 2:

Number of DLTs	≥ 2	≥ 3	≥ 4
Number of Treated Subjects	≤ 4	≤ 6	≤ 8

If the rules for pausing enrollment are met, no further enrollment to the respective dose level/schedule will be allowed until after a careful review of all safety data by the DLRT. Additionally, enrollment will not resume until the protocol has been amended to include additional safeguards for subject safety (eg, modifications to dose level and schedule).

Subjects with EM disease will be able to enroll into cohort 2 after the safety evaluation is complete for 3 subjects with EM disease treated at 400 µg/day (cohort 1). An investigator will review efficacy data and assess outcomes in accordance with IMWG criteria. Investigator assessments will be used for primary efficacy analysis.

Number of Subjects

Approximately 20 subjects will be enrolled in this study.

Summary of Subject Eligibility Criteria

Male or female subjects ≥ 18 years of age at the time of informed consent who have multiple myeloma relapsed after and/or refractory to ≥ 3 lines of established and available therapies with known clinical benefit, including a PI, an immunomodulatory drug, and a CD38-directed monoclonal antibody. Subjects must have measurable disease at screening as defined in the inclusion criteria and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. For a full list of eligibility criteria, refer to Section 6.1 and Section 6.2.

Treatments

AMG 420 will be administered as a continuous intravenous (cIV) infusion. A treatment cycle consists of a 4-week infusion period followed by a 2-week infusion-free interval prior to the following treatment cycle (phase 1b, monotherapy).

Phase 1b dosing for Cohort 1:

Subjects in cohort 1 will receive a dose of 400 µg/day starting on day 1 of each treatment cycle.

Phase 1b dosing for Cohort 2:

Subjects in cohort 2 will receive a dose of 200 µg/day for the first 3 days of treatment cycle 1. On day 4 of cycle 1 and for the remainder of cycle 1, the dose for cohort 2 will then be escalated (dose step) to 600 µg/day. From cycle 2 onwards, the dose will remain at 600 µg/day and no dose step will be required.

Subjects with EM disease will be able to enroll into cohort 2 after the safety evaluation is complete for 3 subjects with EM disease treated at 400 µg/day (cohort 1).

In no case may initial treatment be continued beyond the end of the LTFU period of the last subject in the study.

Inpatient Dosing/Hospitalization:

Minimum hospitalization times for subjects will be as follows:

- Cycle 1: 48 hours or 6 days after start of infusion if step dosing is utilized.
- Cycle 2: 24 hours monitoring after start of infusion; longer monitoring can be decided upon at investigator's discretion.
- Cycles 3 and 4: 4 hours monitoring after start of infusion.
- Cycle 5 and subsequent cycles: hospitalization not required unless subject experiences an adverse event requiring hospitalization as described in Section 7.1.1.4.1 of the study protocol or if clinically indicated. The length of hospitalization required in these cases is to be determined by the investigator.
- Re-start of treatment after an interruption due to adverse event: 48 hours.
- Re-start of treatment after an interruption of > 4 hours due to technical/logistical issue: 24 hours.
- Any cycle with dose re-escalation: 48 hours after dose re-escalation.

For cycles 1 and 2 in-hospital administration, study sites must have immediate access to a medical intensive care unit staffed by critical care providers.

Outpatient Dosing:

If deemed stable by the investigator, a subject may continue AMG 420 cIV infusion as an outpatient.

For infusion bag changes in the outpatient setting, the subject will either return to the study site or be visited by a well-trained home health care service (HHCS) provider at the required frequency. If home visits for IV bag changes are required, the HHCS provider will change the infusion bag, measure vital signs, monitor, document and report adverse events/serious adverse events per Section 9.2.3, and document any issues with the cIV infusion or infusion pump. The subject and HHCS provider will be trained and will receive written instructions for storage of the IV bags, if applicable. The HHCS provider will complete the study delegation log and will be authorized by the investigator before any study-related tasks are started.

Procedures

After providing informed consent, eligible subjects will undergo the following assessments during this study: physical examination, neurological examination, ECOG performance status, height, weight, vital signs, pulse oximetry, ECG triplicate measurement, laboratory assessments (including serum pregnancy test, if applicable, coagulation, hematology, chemistry, urinalysis, hepatitis serology, immunoglobulins, latent tuberculosis test, and [redacted] test), biomarker and PK assessments (including plasmacytoma biopsy for extramedullary disease), and multiple myeloma response assessments including bone marrow (BM) aspirate/biopsy as well as imaging assessments and multiple myeloma serum and urine panels. Reporting of

adverse events, serious adverse events, and cases of pregnancy and lactation will be performed as described in Section 9.2.3.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Section 2.2.

Statistical Considerations

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 420. An overall assessment of safety with monotherapy treatment will be conducted on the Monotherapy Safety Analysis Set defined as all subjects that are enrolled in the study and receive at least 1 dose of AMG 420. The analysis of DLT will be restricted to DLT-evaluable subjects (see Section 7.4.1). The analysis of duration of response (DOR) will be restricted to subjects with a partial response or better. 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 primary endpoints in phase 1b are safety endpoints. Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the Safety Analysis Set, which includes subjects that are enrolled and received at least 1 dose of AMG 420. Interim analyses of safety data will also be conducted on an ongoing basis with the possibility of early termination of enrollment.

Minimal residual disease negative rate, progression-free survival (PFS) and overall survival (OS) analyses will be done for all subjects included in the Full Analysis Set. Duration of response (DOR) and time to response analyses will be done for subjects who are in Full Analysis Set and have a best overall response (BOR) of PR or better. Kaplan-Meier (KM) proportions at select time points, KM quartiles (when estimable) and KM curves will be provided for duration of response, PFS and OS. Descriptive statistics including mean, median, SD, and range will be provided for time to response. Listings will be produced for all subjects indicating the MRD negativity, OS, PFS, time to response, and DOR.

The primary analysis will occur when the target enrollment is complete and each subject has had the chance to be treated for at least 6 months.

A final analysis is planned after all subjects have ended the study.

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

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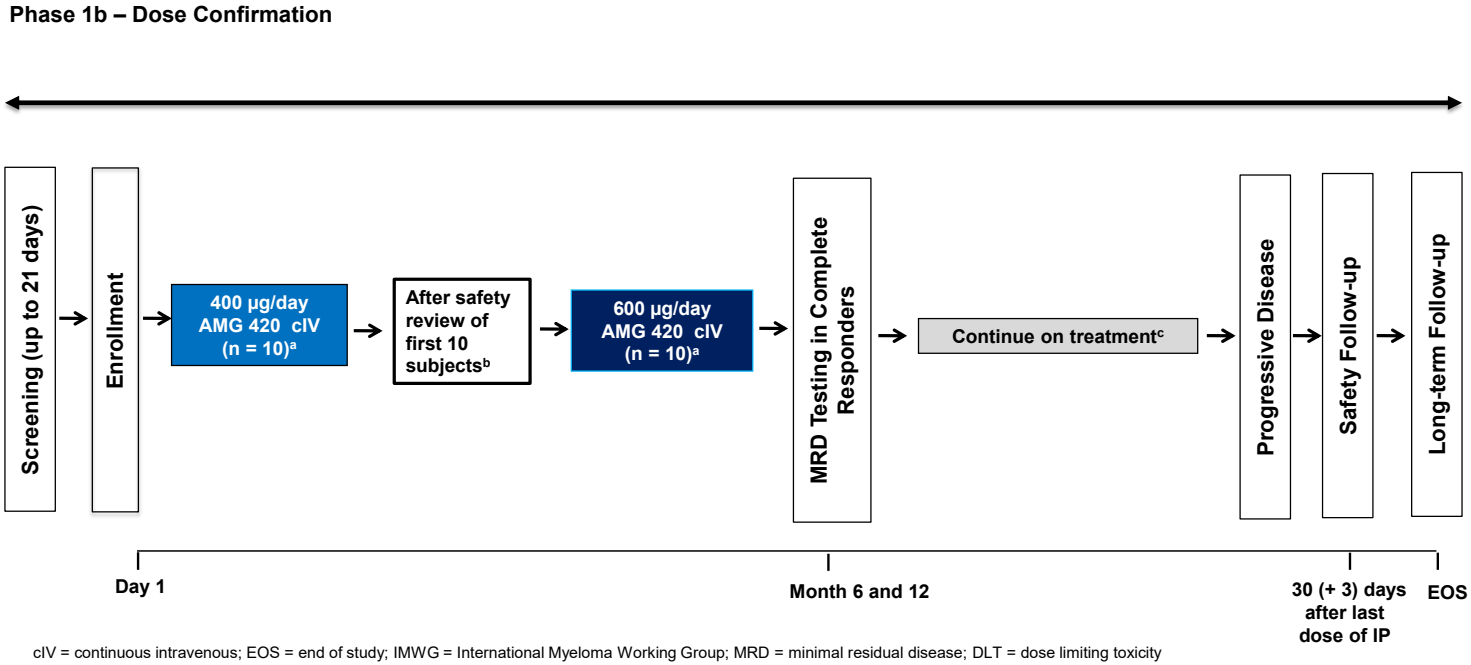
2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema for Monotherapy Dosing



cIV = continuous intravenous; EOS = end of study; IMWG = International Myeloma Working Group; MRD = minimal residual disease; DLT = dose limiting toxicity
[a] Subjects will continue to receive treatment until progressive disease (PD) or relapse as defined by IMWG response criteria, unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation.
[b] At least 30 (+3) days of safety follow-up for each subject.
[c] Subjects attaining MRD-negative responses at 6 and 12 months will be able to increase treatment-free interval.

2.2 Schedule of Activities

Table 2-1. Phase 1b Screening and Treatment Cycle 1 (With No Dose Step)

	SCR	Treatment Period																		
Cycle		1																		Infusion-free Interval[a]
Cycle Day	-21 to -1	1										2	3	4	5	6	8	15	22	29	36
Hours		Pre-dose	Relative to start of infusion																		
			0	1	2	4	6	8	12	16	20	24	48								
GENERAL AND SAFETY ASSESSMENTS																					
Informed consent	X																				
In-/Exclusion criteria	X																				
Demographics/Medical history	X																				
Hospitalization[b]		<---------- 48 hours ---------->																			
Concomitant medications	<---------- continually from informed consent until SFU ---------->																				
SAE review	<---------- continually from informed consent until SFU ---------->																				
AE review			<---------- continually from first dose of AMG 420 until SFU ---------->																		
Physical examination	X	X										X	X				X	X	X	X	X
Peripheral Neuropathy	X																				
ECOG performance status	X	X																		X	
Height	X																				
Weight	X	X																			
Vital signs, pulse oximetry[c]	X	X		X	X	X	X	X	X	X	X	X	X				X	X	X	X	X
ECG triplicate measurement[c]	X	X										X	X							X	

Footnotes defined after last page of table.

Table 2-1. Phase 1b Screening and Treatment Cycle 1 (With No Dose Step)

	SCR	Treatment Period

Cycle		1																		Infusion-free Interval[a]
Cycle Day	-21 to -1	1									2	3	4	5	6	8	15	22	29	36
Hours		Pre-dose	Relative to start of infusion																	
			0	1	2	4	6	8	12	16	20	24	48							
LABORATORY ASSESSMENTS																				
Pregnancy test[d]	X	X																		
Coagulation[e]	X	X						X				X	X				X	X	X	X
Hematology, chemistry[e]	X	X						X				X	X				X	X	X	X
Creatinine Clearance	X																			
Ferritin[f]		X	<–––––––––––––––––––––––––– continue monitoring in case of CRS only ––––––––––––––––––––––––––>																	
Hepatitis serology	X																			
Latent TB test	X																			
Urinalysis	X	X											X				X	X	X	X
Ig: IgA, IgM, IgG	X	X																		
[redacted]		[redacted]																		
PK ASSESSMENTS																				
AMG 420 PK collection[g]		X										X	X				X	X		X[g]

Footnotes defined after last page of table.

Table 2-1. Phase 1b Screening and Treatment Cycle 1 (With No Dose Step)

	SCR	Treatment Period																		
Cycle		1																		Infusion-free Interval[a]
Cycle Day	-21 to -1	1									2	3	4	5	6	8	15	22	29	36
Hours		Pre-dose	Relative to start of infusion																	
			0	1	2	4	6	8	12	16	20	24	48							
DISEASE ASSESSMENTS																				
SPEP/SIFE[h]	X	X																	X	
UPEP/UIFE[h]	X	X																	X	
sβ-2 microglobulin	X																		X	
sFLC (κ/λ)	X	X																	X	
BM aspirate/biopsy[i]	X	At initial suspected CR and at 6 (after 4 cycles) months and repeat at 12 months for subjects who continue to appear to be in CR and recommended in case of PD/relapse																		
% MM involvement[i]	X	At initial suspected CR and at 6 (after 4 cycles) months and repeat at 12 months for subjects who continue to appear to be in CR and recommended in case of PD/relapse																		
BM FISH/karyotyping	X																			
Extramedullary plasmacytoma assessments[j]	X	<–––––– repeat only to confirm a PR or better only if measurable plasmacytoma present at baseline, every 12 weeks (± 2 weeks), as clinically indicated ––––––––>																		
Skeletal survey[j]	X	<–––––– repeat only as clinically indicated ––––––––>																		

Footnotes defined after last page of table.

Table 2-1. Phase 1b Screening and Treatment Cycle 1 (With No Dose Step)

	SCR	Treatment Period																				
Cycle		1																				Infusion-free Interval[a]
Cycle Day	-21 to -1	1										2	3	4	5	6	8	15	22	29		36
Hours		Pre-dose	Relative to start of infusion																			
			0	1	2	4	6	8	12	16	20	24	48									
BIOMARKER ASSESSMENTS																						
[redacted]																						
INVESTIGATIONAL PRODUCT DOSING																						
AMG 420 cIV infusion			————--------->																			
Premedication[o]		X																				

Footnotes defined on next page

AE = adverse event; [redacted] cIV = continuous intravenous; CR = complete response; CRS = cytokine release syndrome; CT = computed tomography; [redacted] ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; FISH = fluorescent in situ hybridization; Ig = immunoglobulins; MDSCs = myeloid derived suppressor cells; MM = multiple myeloma; MRD = minimal residual disease; MRI = magnetic resonance imaging; [redacted] PD = progressive disease; PET = positron emission tomography; [redacted] PK = pha[redacted]se; SAE = serious adverse event; [redacted] SCR = screening; sFLC (κ/λ) = serum free light chain (kappa/lambda); SFU = safety follow-up; SIFE = serum immunofixation; SPEP = serum protein electrophoresis; TB = tuberculosis; UIFE = urine immunofixation; UPEP = urine protein electrophoresis

[a] Infusion-free interval = days 30 to 42, day 43 = day 1 of subsequent cycle.

[b] See Section 7.1.1.4.1 for details on hospitalization requirements.

[c] ECGs and vital signs should be performed approximately 15 min prior to any invasive procedures including IV bag change, if applicable, and approximately 15 min prior to EOI. ECGs are only required in cycle 1 and 2.

[d] Refer to Section 9.2.4.1 for details of required pregnancy testing.

[e] As indicated in Section 12.2, hematology and chemistry panels include differential cell counts and comprehensive metabolic profile, as well as serum uric acid and phosphorous levels, and liver function tests. Coagulation panel includes prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and D-dimer.

[f] If ferritin value after CRS is abnormal, continue monitoring until values are back to baseline/event is resolved.

[g] Time schedule for PK sampling cycle 1 day 29: approximately 15 min prior to EOI and 4, 8, 24, and 48 hours after EOI.

[h] Serum and urine immunofixation (IFE) for M-protein measurements. Urine IFE to be only followed up if positive for M protein at baseline.

[redacted]

Baseline imaging is required at screening (if done within 30 days prior to screening for standard of care, no need to repeat) to evaluate for extramedullary (EM) relapse using whole body MRI or PET/CT and should be repeated during treatment only to confirm a PR or better only if measurable plasmacytoma are present at baseline every 12 weeks (± 2 weeks) and as clinically indicated. Skeletal survey does not need to be performed at screening if CT or PET CT performed and does not need to be repeated after screening unless clinically indicated.

[k] MRD and [redacted]

[l] Collection of samples on day 29 should be done prior to EOI.

[redacted]

See Section 7.1.4 for details on premedication requirements.

Table 2-2. Phase 1b Treatment Cycle 2, 3, and Following to End of Study

	Treatment Period															Follow-up Period	
Cycle	2							Infusion-free Interval[a]	3 and all subsequent cycles					Infusion-free Interval[a]	EOT	SFU	LTFU[b,v]
Cycle Day	1		2	8	15	22	29	36	1	8	15	22	29	36		30 (+3) days	Up to 5 yrs after first dose of IP, or subject death, whichever occurs first
Hours	Pre-dose	Relative to start of infusion							Pre-dose	Relative to start of infusion							
		6	24							4							
GENERAL AND SAFETY ASSESSMENTS																	
Hospitalization[c]	---------->								------->								
Concomitant medications	<---------- continually from informed consent until SFU ---------->																
Subsequent anti-MM treatment																X	X
SAE review	<---------- continually from informed consent until SFU ---------->																X[d]
AE review	<---------- continually from first dose of AMG 420 until SFU ---------->																
Physical examination	X		X	X	X	X	X	X	X							X	X	
Peripheral neuropathy	X								X									
ECOG performance status	X						X		X					X		X	X	
Weight	X								X							X	X	
Vital signs, pulse oximetry[e]	X[f]	X[f]	X	X	X	X	X	X	X[g]	X[g]	X	X	X	X		X	X	
ECG triplicate measurement[e]	X		X				X									X	X	

Footnotes defined after last page of table.

Table 2-2. Phase 1b Treatment Cycle 2, 3, and Following to End of Study

	Treatment Period															Follow-up Period	
Cycle	2							Infusion-free Interval[a]	3 and all subsequent cycles					Infusion-free Interval[a]	EOT	SFU	LTFU[b,v]
Cycle Day	1		2	8	15	22	29	36	1		8	15	22	29	36		30 (+3) days	Up to 5 yrs after first dose of IP, or subject death, whichever occurs first
Hours	Pre-dose	Relative to start of infusion							Pre-dose	Relative to start of infusion								
		6	24							4								
LABORATORY ASSESSMENTS																		
Coagulation[h]	X		X	X	X	X	X		X		X	X	X			X	X	
Hematology, chemistry[h]	X		X	X	X	X	X		X		X	X	X			X	X	
Ferritin[i]	<---------- continue monitoring in case of CRS only ---------->																	
Urinalysis	X						X		X		X					X	X	
Ig: IgA, IgM, IgG	X															X		X
[redacted]	[redacted]								[redacted]								[redacted]	
PK ASSESSMENTS																		
AMG 420 PK collection	X		X	X	X		X[k]		X					X[k]				

Footnotes defined after last page of table

Table 2-2. Phase 1b Treatment Cycle 2, 3, and Following to End of Study

	Treatment Period															Follow-up Period	
Cycle	2						Infusion-free Interval[a]	3 and all subsequent cycles					Infusion-free Interval[a]	EOT	SFU	LTFU[b,v]
Cycle Day	1	2	8	15	22	29	36	1	8	15	22	29	36		30 (+ 3) days	Up to 5 yrs after first dose of IP, or subject death, whichever occurs first
Hours	Pre-dose	Relative to start of infusion: 6	Relative to start of infusion: 24					Pre-dose	Relative to start of infusion: 4							
DISEASE ASSESSMENTS																
SPEP/SIFE[l]	X							X						X	X	X
UPEP/UIFE[l]	X							X						X	X	X
sβ-2 microglobulin								X								
sFLC (κ/λ)	X							X						X	X	X
BM aspirate/biopsy[m]	At initial suspected CR and at 6 (after 4 cycles) months and repeat at 12 months for subjects who continue to appear to be in CR and recommended in case of PD/relapse															
% MM involvement[m]	At initial suspected CR and at 6 (after 4 cycles) months and repeat at 12 months for subjects who continue to appear to be in CR and recommended in case of PD/relapse															
Skeletal survey/ plasmacytoma assessments[n]	<——— repeat only to confirm a PR or better only if measurable plasmacytoma present at baseline, every 12 weeks (± 2 weeks), as clinically indicated ———>															
BIOMARKER ASSESSMENTS																
[redacted]																

Footnotes defined after last page of table.

Table 2-2. Phase 1b Treatment Cycle 2, 3, and Following to End of Study

	Treatment Period														Follow-up Period	
Cycle	2						Infusion-free Interval[a]	3 and all subsequent cycles					Infusion-free Interval[a]	EOT	SFU	LTFU[b,v]
Cycle Day	1	2	8	15	22	29	36	1	8	15	22	29	36		30 (+3) days	Up to 5 yrs after first dose of IP, or subject death, whichever occurs first
Hours	Pre-dose	Relative to start of infusion						Pre-dose	Relative to start of infusion							
		6	24						4							
BIOMARKER ASSESSMENTS (continued)																
[redacted]																
INVESTIGATIONAL PRODUCT DOSING																
AMG 420 cIV infusion	---------->							---------->								
Premedication[t]	X							X								

Footnotes defined on next page

AE = adverse event; [redacted]; cIV = continuous intravenous; CR = complete response; CRS = cytokine release syndrome; CT = computed tomography; [redacted] ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = end of treatment; EOS = end of study; Ig = immunoglobulins; IP = investigational product; LTFU = long-term follow-up; MDSCs = myeloid derived suppressor cells; MM = multiple myeloma; MRD = minimal residual disease; MRI = magnetic resonance imaging; [redacted] PB = peripheral blood; PD = progressive disease; PET = positron emission tomography; [redacted]; PK = pharmacokinetics; PR = partial response; SAE = serious adverse event; [redacted]; sFLC (κ/λ) = serum free light chain (kappa/lambda); SFU = safety follow-up; SIFE = serum immunofixation; SPEP = serum protein electrophoresis; UIFE = urine immunofixation; UPEP = urine protein electrophoresis

[a] Infusion-free interval = days 30 to 42, day 43 = day 1 of subsequent cycle. In case of extended treatment-free interval (treatment holiday), an on-site visit should be performed within one week prior to re-start of study treatment, assessments will be performed as on day 36 of cycle 1 (see Schedule of Assessment Table 2-1).

[b] LTFU via on-site visit every 6 weeks (± 7 days) until progression of disease. Afterwards, LTFU frequency will be 3 months for collecting information on survival and subsequent anti-MM treatment only, without the requirement for on-site visits.

[c] See Section 7.1.1.4.1 for details on hospitalization requirements.

[d] See Sections 9.2.3.1 and 12.4 for SAE reporting requirements during LTFU.

[e] ECGs and vital signs should be performed approximately 15 min prior to any invasive procedures including IV bag change, if applicable, and approximately 15 min prior to EOI. ECGs are only required in cycle 1 and 2.

[f] Cycle 2 day 1: vital signs measurement also required 1, 2, and 4 hours after infusion start.

[g] Cycle 3 and 4 day 1: vital signs measurement also required 1 and 2 hours after infusion start.

[h] As indicated in Section 12.2, hematology and chemistry panels include differential cell counts and comprehensive metabolic profile, as well as serum uric acid and phosphorous levels, and liver function tests. Coagulation panel includes prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and D-dimer.

[i] If ferritin value after CRS is abnormal, continue monitoring until values are back to baseline/event is resolved.

[redacted]

[k] PK sampling should be done approximately 15 min prior to EOI.

[l] Serum and urine immunofixation (IFE) for M-protein measurements. Urine IFE to be only followed up if positive for M-protein at baseline.

[redacted]

[n] Plasmacytoma assessments are to be repeated during treatment only to confirm a PR or better only if measurable plasmacytoma are present at baseline, to confirm PD, at initiation of other anti-MM treatment, or if clinically indicated. The same technique (may include MRI, PET-CT, or other standard-of-care method) must be employed for each measurement. Skeletal survey is not required for confirmation of PR or better.

[o] MRD and [redacted]

[t] See Section 7.1.4 for details on premedication requirements.

[redacted]

During the Long-term follow-up phase serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen.

3. Introduction

3.1 Study Rationale

3.1.1 Target Rationale

B-cell maturation antigen (BCMA, TNFRSF17, CD269) is a tumor necrosis factor (TNF) receptor superfamily member and a type III integral membrane protein (Madry et al, 1998). BCMA expression on normal tissues is highly restricted to the B-cell lineage where it is predominately expressed in the secondary follicle/germinal center of tonsils/lymph nodes (Chiu et al, 2007), on plasmablasts (Avery et al, 2003), and on differentiated plasma cells (O'Connor et al, 2004). Analysis of BCMA mRNA and protein expression in human tissues indicated that, except for plasma cells, BCMA is not detectably expressed in normal human tissues (Carpenter et al, 2013). The biological function of BCMA, promoting the survival of plasma cells, is mediated via binding to its ligands: a proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF) (Yu et al, 2000). In addition to BCMA, APRIL binds to transmembrane activator and calcium modulator (TACI) and BAFF binds to B-cell activating factor receptor (BAFF-R) (Thompson et al, 2001; Gross et al, 2000). Both APRIL and BAFF are expressed predominately by myeloid-derived cells including macrophages, dendritic cells, and neutrophils that form part of the bone marrow (BM) stroma and also reside in lymphoid organs. Disruption of the BCMA/BAFF-APRIL interaction in mice deficient for BCMA results in decreased survival of long-lived plasma cells (Avery et al, 2003).

B-cell maturation antigen is expressed at relatively higher levels on malignant plasma cells (multiple myeloma) than the level observed on normal plasma cells (Zhao et al, 2008). Multiple independent analyses of mRNA in primary human multiple myeloma samples indicate that all multiple myeloma patients' samples have high levels of BCMA (Tai et al, 2006; Moreaux et al, 2004). The high prevalence of BCMA expression in multiple myeloma has been confirmed at the protein level by immunohistochemistry or flow cytometry, which demonstrated cell-surface BCMA expression in neoplastic plasma cells from all patients with multiple myeloma tested (Carpenter et al, 2013; Novak et al, 2004). For this phase 1 trial, relapsed and/or refractory multiple myeloma (RRMM) has been chosen as the indication to pursue with AMG 420 because of the near 100% incidence of BCMA expression in this patient population.

3.1.2 Target Population Rationale

The 5-year survival rate for multiple myeloma has improved from approximately 25% for newly diagnosed patients in 1975 to approximately 50% in 2013 (SEER, 2014). This is mainly attributed to new drugs such as proteasome inhibitors (PIs) and immunomodulators (IMiDs). Most recently, daratumumab has been approved for RRMM and is likely to further improve long-term outcomes. Patients refractory to PIs and IMiDs have a poor prognosis with a median OS of 9 months with further treatment and 3 months without (Kumar et al, 2012). Outcome is particularly poor in molecularly defined populations such as the high-risk subgroup del17p13 positive multiple myeloma (Avet-Loiseau et al, 2007). Daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, has substantially improved PFS and overall response rate (ORR) for previously treated patients with multiple myeloma, regardless of prior treatment exposure or cytogenetic risk (Dimopoulos et al, 2016; Palumbo et al, 2016). However, there is still a significant need for new therapies for multiple myeloma patients, particularly as the vast majority of disease responses are transient in nature with existing therapies and there remains no established cure for this malignancy (Carpenter et al, 2013; Novak et al, 2004).

3.2 Background

3.2.1 Disease

Multiple myeloma is a neoplastic plasma-cell disorder characterized by clonal proliferation of malignant plasma cells in the BM microenvironment, monoclonal protein in the blood or urine and associated organ dysfunction (Palumbo and Anderson, 2011). Multiple myeloma accounts for almost 2% of all cancers and 20% of hematologic malignancies. The disease is slightly more common in males and African Americans (Siegel et al, 2015). Multiple myeloma remains an incurable cancer, although recent improved understanding of pathogenesis of myeloma has led to the development of new treatments and improved survival (Smith and Yong, 2013).

Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post–germinal-center B-cells. Multistep genetic and micro-environmental changes lead to the transformation of these cells into a malignant neoplasm. Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance (usually known as MGUS) that progresses to smoldering myeloma and, finally, to symptomatic myeloma. The diagnosis of multiple myeloma requires the presence of 1 or more myeloma defining

events (MDE) in addition to evidence of either 10% or more clonal plasma cells on BM examination or a biopsy-proven plasmacytoma. Myeloma defining events consist of established CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions) features as well as 3 specific biomarkers: clonal BM plasma cells ≥ 60%, serum free light chain (sFLC) ratio ≥ 100 (provided involved sFLC level is ≥ 100 mg/L), and more than 1 focal lesion on magnetic resonance imaging (MRI) (Rajkumar et al, 2014). Several genetic abnormalities that occur in tumor plasma cells play major roles in the pathogenesis of myeloma and determine disease prognoses (Palumbo and Anderson, 2011).

The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, BM failure, increased plasma volume and viscosity, suppression of normal immunoglobulin (Ig) production, and renal insufficiency (Durie, 2011).

Symptomatic (active) disease should be treated immediately, whereas asymptomatic (smoldering) myeloma requires only clinical observation, since early treatment with conventional chemotherapy has shown no clear benefit yet. Investigational trials are currently evaluating the ability of IMiDs to delay the progression from asymptomatic to symptomatic myeloma. For active myeloma, current data support the initiation of induction therapy regimens including thalidomide, lenalidomide, and/or bortezomib followed by autologous hematopoietic stem cell transplantation (HSCT) after major disease response for many patients who can tolerate auto-HSCT conditioning regimens. Considerations of physiologic age, which may differ from chronologic age, and the presence of coexisting conditions drive decisions of treatment choice and drug dose (Palumbo and Anderson, 2011). For example, less intensive approaches are desirable for patients with significant comorbidities, including cardiopulmonary or hepatic impairment, limiting treatment-related mortality, and mitigating risk of treatment interruption.

Treatment of RRMM presents a special therapeutic challenge, due to the heterogeneity of disease at relapse and the absence of clear biological based recommendations regarding the choice of salvage therapies at various time points of disease progression. With increasing recognition of the inherent clonal heterogeneity and genomic instability of the plasma cells influencing both inherent and acquired therapeutic resistance, the identification of the optimal choice and sequence of therapies has become critical. Several new agents and targets are currently under development and show considerable promise. Besides carfilzomib and pomalidomide that were granted approval by United States (US) Food and Drug Administration (FDA) in 2012 and 2013, respectively, for

RRMM, the next generation PIs (ixazomib, marizomib, and oprozomib), other molecularly targeted therapies directed at specific cell signaling pathways (including histone deacetylase inhibitors, PI3K/AKT/mTOR inhibitors, Hsp90 inhibitors, cell cycle inhibitors, kinesin spindle protein inhibitors) are currently in development. The first monoclonal antibodies targeting SLAMF7 (elotuzumab) and CD38 (daratumumab) have recently been granted approval. Emplicity™ (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received 1 to 3 prior therapies. The 1- and 2-year rates of PFS for elotuzumab in combination with lenalidomide and dexamethasone treatment were 68% and 41%, respectively, compared with 57% and 27%, respectively, for lenalidomide and dexamethasone treatment in the corresponding phase 3 trial (Lonial et al, 2015). Darzalex® (daratumumab) approval was based on the pivotal phase 3 POLLUX and CASTOR clinical studies. Daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, substantially improved PFS and ORRs for previously treated patients with multiple myeloma, regardless of prior treatment exposure or cytogenetic risk. Daratumumab with lenalidomide and dexamethasone lowered the risk of disease progression or death by 64%, compared with lenalidomide and dexamethasone alone, in patients with multiple myeloma who had received 1 to 3 prior lines of therapy. Daratumumab with bortezomib and dexamethasone reduced the risk of disease progression or death by 61% in similar patients, compared with bortezomib and dexamethasone alone (Dimopoulos et al, 2016; Palumbo et al, 2016). Even newer approaches such as chimeric antigen receptor (CAR) T-cells, antibody-drug conjugates, and bispecific antibodies targeting BCMA have also demonstrated first promising anti-myeloma activity (Berdeja et al, 2016; Cohen et al, 2016; Panowski et al, 2016). Despite advances in the management of multiple myeloma as described, relapse is inevitable in almost all patients. Recurrence of myeloma is typically more aggressive with each relapse, leading to the development of treatment refractory disease, which is associated with a shorter survival (Dimopoulos et al, 2015). Thus, additional treatment options are warranted.

3.2.2 Amgen Investigational Product Background: AMG 420

AMG 420 (formerly known as Boehringer Ingelheim [BI] investigational product BI 836909) is a member of a novel class of bispecific antibody constructs called “bispecific T-cell engagers” or BiTE® antibody constructs (Frankel and Baeuerle, 2013). They have been designed to direct T cells towards target cells. The proximity induced

by the BiTE® antibody construct triggers target cell specific cytotoxicity which closely resembles standard cytotoxic T lymphocyte activation.

AMG 420, targeting the surface antigen BCMA, is a novel BiTE® antibody construct which is being developed with the intent to treat patients with multiple myeloma. T cells are bound by its anti-CD3 moiety, whereas multiple myeloma cells are bound by the anti-BCMA moiety. This unique feature of AMG 420 allows it to transiently connect malignant cells with T cells, thereby inducing T-cell mediated killing of the bound malignant cell. In preclinical models, AMG 420-mediated T-cell activation involves the transient release of inflammatory cytokines and proliferation of T cells. The subsequent serial lysis of multiple malignant cells by a single AMG 420-activated T cell closely resembles a natural cytotoxic T-cell reaction.

A phase 1 first-in-human (FIH) dose-escalation study with AMG 420, conducted by BI to estimate the maximum tolerated dose (MTD), is currently ongoing (BI study number 1351.1, NCT02514239) with 400 μg/day defined as a safe and effective dose, with DLTs identified in 2 of 3 subjects treated at the next dose that was tested, 800 μg/day.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AMG 420 is provided in the AMG 420 Investigator's Brochure.

3.2.2.1 Nonclinical Pharmacology

In vitro Pharmacology

AMG 420 is a highly potent molecule selectively mediating redirected lysis of $BCMA^+$ cells, while viability of target-negative cells remains unaltered. The cytotoxic effect of AMG 420 is time- and dose-dependent, with mean concentrations inducing half-maximal target cell lysis (EC_{50}) ranging from 5 pg/mL to 2011 pg/mL with human effector cells.

In the presence of target cells, AMG 420 induced a polyclonal activation of T cells, which resulted in an up-regulation of the T-cell activation markers CD25 and CD69, induction of granzyme B and perforin synthesis, T cell proliferation and release of cytokines like interferon-γ (IFN-γ), TNF, interleukin (IL)-2 and IL-10.

B-cell maturation antigen can be shed from the cell surface and was found in serum samples of multiple myeloma patients as well as in healthy subjects (Sanchez et al, 2012). Median serum concentrations were higher in multiple myeloma patients (17.79 ng/mL) than in healthy blood donors (2.57 ng/mL) and highest levels

were observed in patients with progressive disease (PD) (19.76 ng/mL; Sanchez et al, 2012). A more recent publication demonstrated that soluble BCMA (sBCMA) levels correlated with the proportion of plasma cells in BM biopsies, clinical status and can be tracked with changes in M-protein levels. In this study, healthy donors had a median sBCMA blood concentration of 36.8 ng/mL, similar to median levels observed in patients with complete response (CR) (38.9 ng/mL). Patients with smoldering multiple myeloma had higher concentrations (median 88.9 ng/mL); whereas patients with active untreated multiple myeloma had highest levels (median 505.9 ng/mL). With a median of 9.0 versus 3.6 months, PFS was longer for patients with sBCMA levels below the median (326.4 ng/mL) when compared with those with levels above the median (Ghermezi et al, 2017).

The impact of sBCMA on AMG 420-induced cytotoxicity and T-cell activation was evaluated in co-cultures of BCMA-positive tumor cells, human peripheral blood mononuclear cell (PBMC), and recombinant human sBCMA, which is a 50-amino acid polypeptide (5.3 kDa) region of the BCMA protein (Sigma-Aldrich) at concentrations up to 400 ng/mL. Although maximal target cell lysis was not affected by sBCMA, EC_{50} values increased with increasing sBCMA concentrations.

Ex vivo, an AMG 420-mediated depletion of $BCMA^+$ cells by autologous T cells was observed in a BM aspirate from a multiple myeloma patient.

In vivo Pharmacology

The anti-tumor activity of AMG 420 was evaluated in multiple myeloma xenograft models.

In an orthotopic multiple myeloma model non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice were intravenously (IV) injected with L-363 tumor cells. AMG 420 significantly prolonged survival of animals at dose levels of 0.005, 0.05, and 0.5 mg/kg/day when **IV** administered for 26 consecutive days.

In a second xenograft model NOD/SCID mice were subcutaneously (SC) injected with NCI-H929 multiple myeloma tumor cells. AMG 420 inhibited SC tumor growth when administered for 19 consecutive days at IV dose levels of 0.5 or 0.05 mg/kg/day or SC administration at 4 or 0.4 mg/kg/day.

3.2.2.2 Pharmacokinetics

Non-clinical Pharmacokinetics

The toxicokinetics of AMG 420 was investigated in a 7-day dose range-finding cIV infusion or SC injection toxicity and toxicokinetic study in the cynomolgus monkey. The dose levels were 0, 5, 15, 45, and 135 µg/kg/day by cIV infusion and 135 and 405 µg/kg/day by once-daily SC injection. Blood samples for toxicokinetics were collected on drug day 0 and 7 for the cIV infusion doses and drug days 0 and 6 for the SC doses. Serum samples were analyzed for AMG 420 concentrations using an electrochemiluminescence method with a lower limit of quantification of 0.5 ng/mL. AMG 420 exposure (maximum concentration [C_{max}] and area under the concentration-time curve from time 0 to the last measurable concentration [AUC_{last}]) increased approximately proportionally to the increase in dose level. There was no apparent sex difference in exposure.

The toxicokinetics of AMG 420 was also investigated in a 4-week cIV infusion and SC toxicity study in the cynomolgus monkey. The dose levels were 0, 15, 45, and 135 µg/kg/day using cIV infusion and 405 µg/kg/day using once-daily SC injection. Blood samples for toxicokinetics were collected on study days 2, 7, 14, 21, and 27 for both the cIV and SC dose groups. AMG 420 exposure increased approximately proportionally to the increase in dose level in the cIV dose groups. There was no consistent accumulation of AMG 420 exposure upon cIV dosing for 28 days, whereas a slight accumulation of AMG 420 exposure upon repeated SC dosing was observable. There was no apparent sex difference in exposure in both the cIV and SC dose groups.

Clinical Pharmacokinetics

AMG 420 concentration data were collected from 34 subjects with RRMM in the ongoing AMG 420 FIH study, Study 1351.1. AMG 420 was dosed as a continuous IV (cIV) infusion for 4 weeks, in escalating dose levels ranging from 0.2 µg/day to 800 µg/day.

Following cIV infusion of AMG 420, free steady-state concentrations (Css) were reached in approximately 2 days and remained stable over the infusion period. Mean free AMG 420 Css values increased with increasing dose.

Please refer to the Investigator's Brochure for further details of preliminary PK analyses for AMG 420.

3.2.2.3 Toxicology

The nonclinical safety assessment of AMG 420 was conducted in cynomolgus monkey by cIV infusion or SC administration and consisted of 7- and 28-day repeat-dose toxicology studies. Results hereafter refer to cIV dosing in the Good Laboratory Practice (GLP) 28-day repeat-dose toxicology study; the toxicological profile of the two routes of administration was similar at the highest doses tested (135 µg/kg cIV and 405 µg/kg SC). In the 28-day GLP study, a dose of 135 µg/kg/day resulted in moribundity/mortality; two animals were euthanized during the study due to either complications with the catheterization site or hypothermia and decreased activity. In the premature decedents, the pharmacological action of AMG 420 induced a systemic lymphoid depletion intensified by hematological disorders (hemolytic anemia) which enabled the onset of opportunistic secondary infections in some animals that were responsible for their death or moribund condition. Doses of 15 and 45 µg/kg were well tolerated.

At doses ≥ 45 µg/kg/day, emesis, increased body temperature (up to 1.7°C) and increases in serum IL-2, IL-6 and IFN-γ were seen in most animals on the day of treatment initiation (4 to 8 hours after the start of AMG 420 administration) and resolved within 24 to 48 hours.

Serum chemistry evaluations indicated AMG 420-related changes at 24 hours after the initiation of administration and/or on day 28 mostly at 135 µg/kg. These changes consisted of decreased calcium (at ≥ 15 µg/kg), decreased total protein levels (due to decreased albumin and/or globulin levels, at 135 µg/kg), and increased creatinine (135 µg/kg). In addition, a dose-responsive increase in C-reactive protein levels was observed at 24 hours after the start of administration for all dose levels. All changes were generally reversible after a 4-week recovery period.

Large modifications in white blood cell parameters were observed at all dose levels when compared with pretest and control animal values. Most animals treated with AMG 420 showed an initial increase (< 4.4-fold) in absolute neutrophil counts (ANC) at 4 hours after the start of infusion/dosing and decreases (up to 90%) in absolute and/or relative lymphocyte, monocyte, eosinophil, basophil, and large unstained cell counts at 4 to 24 hours. This lymphopenia showed a trend toward reversibility but not full reversal at the end of the treatment period or the recovery period.

Decreases in T and B lymphocytes (≥ 15 µg/kg) and natural killer (NK) cells (≥ 45 µg/kg) were observed at 4 and 24 hours after initiation of treatment with a corresponding decrease in activated ($CD25^+$ and/or $CD69^+$) T lymphocytes at the 4-hour time point at

all dose levels. A further decrease in activated T lymphocytes, B lymphocytes, and NK cells was observed on day 28 at most previously-affected doses. At the end of the recovery period, all lymphocyte subtypes were similar to control values with the exception of low B lymphocytes in one 135 µg/kg male.

AMG 420-related light microscopic findings (eg, lymphoid depletion, increased cellularity) were present in the tonsils, lymph nodes, spleen, and BM (smears) at all dose levels. Histologic effects on sternal BM (increased cellularity) were present at doses ≥ 135 µg/kg/day. The AMG 420-related lymphoid microscopic changes at 135 µg/kg were accompanied by hematological (hemolytic anemia) and inflammatory changes (mainly in the liver) similar to those observed in premature decedents and were, therefore, considered adverse. Inflammatory and hematological changes persisted in 2 animals at the end of the recovery period. At 15 or 45 µg/kg, the lymphoid depletion was considered not adverse due to absence of secondary infections and/or hematological changes; there was evidence of at least partial reversal of lymphoid depletion at the end of the recovery period.

Dose-dependent decreases in BM plasma cells (an expected consequence of the pharmacologic activity of AMG 420) were detected in the BM smears at all doses. At the end of the recovery phase, plasma cell percentages were comparable with those of control animals or were increased relative to the day 28 values, indicating partial to complete recovery.

AMG 420 did not demonstrate any effects on neurological, renal, or cardiovascular functions including electrocardiograms (ECGs) in the 28-day toxicology study.

In conclusion, AMG 420-associated changes in the 28-day toxicology study were generally consistent with the expected BiTE® mode of action and targeting of BCMA. The changes were largely reversible and/or considered nonadverse at the doses ≤ 45 µg/kg. The highest non-severely toxic dose of AMG 420 following daily cIV infusion for 28 days was considered to be 45 µg/kg.

Please refer to the Investigator's Brochure for further details of the toxicology studies performed with AMG 420.

3.2.2.4 Clinical Experience With Other BiTE® Antibody Constructs and AMG 420

BiTE® antibody constructs exert a unique but also uniform mechanism of action independent from their respective target. Consequently, experiences with other BiTE® antibody constructs are regarded as being relevant for AMG 420.

Most clinical experience exists with a BiTE® antibody construct called blinatumomab (BLINCYTO®, AMG 103; specificity for CD3 and CD19), which has shown that administration of BiTE® antibody constructs by cIV infusion is feasible and efficacious in subjects with late-stage hematological malignancies (Yuraszeck et al, 2017; Benjamin and Stein, 2016; Nagorsen et al, 2012). Blinatumomab has demonstrated clinical activity in acute lymphoblastic leukemia (ALL). Clinical responses have been seen in both adults and children (Amgen clinical studies 103-206 [NCT01209286], 103-205 [NCT01471782], 103-211 [NCT01466179], and 00103311/TOWER [NCT02013167]) confirming the activity of BiTE® antibody constructs in B-precursor ALL (Kantarjian et al, 2017; Von Stackelberg et al, 2016; Topp et al, 2015; Topp et al, 2014). Based on these data, blinatumomab is approved in multiple regions for the treatment of Philadelphia chromosome-negative relapsed and/or refractory B-cell precursor ALL.

The most common adverse reactions (≥ 20%) were pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation. According to the US prescribing information, additional adverse reactions included cytokine release syndrome (CRS), neurological toxicities, infections, tumor lysis syndrome (TLS), neutropenia and febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, leukoencephalopathy, and preparation/administration errors.

Several other BiTE® antibody constructs have entered clinical trials. Adverse events common to these constructs and blinatumomab include fever and fatigue. However, the spectrum of neurologic and psychiatric adverse events observed in patients treated with blinatumomab (eg, confusion, disorientation) has not been reported with these constructs to date.

A phase 1, FIH, open-label, dose escalation study (1351.1) is ongoing to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of cIV doses of AMG 420 in subjects with RRMM. AMG 420 is administered as a cIV infusion for 4 consecutive weeks via an indwelling central IV line. After a 2-week treatment-free

period, the subjects receive up to a total of five 4-week on/2-week off courses. If subjects experience continued benefit, up to 5 more courses may be given.

Data from 35 subjects (up to 800 μg/day) were available at the time of data snapshot (22 May 2018). Subjects were treated at doses ranging from 0.2 μg/day to 800 μg/day. In general, AMG 420 was well tolerated. All 35 subjects (100%) had adverse events; 32 of 35 subjects (91.4%) had adverse events grade ≥ 3. The most frequent adverse events were lymphocyte count decreased (21 subjects, 60.0%); anemia (12 subjects, 34.3%); white blood cell count decreased (12 subjects, 34.3%); pyrexia (11 subjects, 31.4%); and CRS (10 subjects, 28.6%). Infections and infestations occurred in 23 subjects (65.7%), most notably device related infections in 7 subjects (20.0%). Thirty-three of 35 subjects (94.3%) had an adverse event considered drug-related by the investigator. The most frequent drug-related adverse events (> 20%) were lymphocyte count decreased (21 subjects, 60.0%) and CRS (10 subjects, 28.6%). Drug-related grade 3 and grade 4 adverse events occurred in 10 subjects (28.6%) and 17 subjects (48.6%), respectively. The most frequent drug-related grade 3 and grade 4 adverse events were lymphocyte count decreased, with 6 subjects (17.1%) reporting grade 3 events and 14 subjects (40.0%) reporting grade 4 events. No drug-related grade 5 events were reported in this study. Serious adverse events were reported in 17 subjects (48.6%). The most frequent serious adverse events were device-related infections, pneumonia, and cytokine release syndrome (CRS) in 3 subjects (8.6%) each. Most subjects reporting serious adverse events had grade 3 adverse events (12 subjects, 34.3%). Drug-related serious adverse events were CRS in 3 subjects (8.6%), and peripheral motor neuropathy, generalized edema, and pyrexia in 1 subject (2.9%) each. Two dose-limiting toxicities (DLTs) were reported in the 800 μg/day cohort; 1 grade 3 CRS and 1 grade 3 peripheral motor neuropathy.

In this FIH trial, 10 of 12 CRS-specific adverse events occurring in 10 subjects were limited to cycle 1 administration of AMG 420 and had an onset within 24 hours of administration. All events of CRS occurring at doses under 800 μg/day were grade 1 by Common Terminology Criteria for Adverse Events (CTCAE) criteria. Two of the 12 CRS-specific adverse events occurred in 2 subjects during cycle 2, were grade 1 in severity, and had an onset within 24 hours of treatment administration.

As of the 22 May 2018 data snapshot, preliminary efficacy data have shown an objective response in 8 subjects (23%). Six subjects achieved a best response of CR as assessed by the investigator using International Myeloma Working Group (IMWG)

response criteria, including 1 each at 6.5, 100, and 200 µg/day, and 3 at 400 µg/day. Four of the 6 CRs (1 at 200 µg/day and 3 at 400 µg/day) were also MRD-negative. As of the data cutoff date, 4 out of the 6 subjects remain in CR (all 4 were MRD-negative). Two additional subjects demonstrated a response to AMG 420; 1 subject at 50 µg/day achieved a partial response (PR) and 1 subject at 800 µg/day achieved a very good partial response (VGPR).

For additional information refer to the current version of the Investigator's Brochure.

A phase 1, FIH, open-label, dose-escalation study (Study 20170122) evaluating the safety, tolerability, PK, and pharmacodynamics of AMG 701 subjects with RRMM is currently ongoing. AMG 701 is a molecule that is related to AMG 420 in that an scFc fragment has been introduced into the canonical BiTE® antibody structure to prolong its half-life. AMG 701, which also shares the same BCMA target as AMG 420, is administered as a short intravenous infusion once weekly. As of 25 November 2019, 1 subject in dose escalation has achieved stringent CR, with AMG 701 treatment at the 800 µg weekly dose. Seven subjects achieved partial responses (PR) or very good PRs (VGPR) out of a total of 19 evaluable enrolled in the 3000, 4500, and 6500 µg target dose cohorts. Out of 4 subjects enrolled in the 6500 µg target dose, 2 subjects have attained VGPRs, 1 subject attained minimal response (MR), and one subject experienced rapid disease progression after receiving the 800 µg run-in dose and never received the target dose. As of 25 November 2019, 7 of 8 clinical responses are continuing, with the longest response lasting over 1 year, and dose exploration/escalation ongoing.

3.3 Benefit/Risk Assessment

At this time, there is limited clinical experience with AMG 420 in humans. Based on nonclinical toxicity studies of AMG 420, and preliminary clinical safety and efficacy experience with AMG 420, the overall benefit/risk profile favors further clinical development of AMG 420 for patients with RRMM. 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. Reference should be made to the Investigator's Brochure for further data on AMG 420.

3.3.1 Therapeutic Context

Multiple myeloma treatment has evolved rapidly in recent years. Progress has been made with the introduction of several breakthrough drugs, including IMiDs and PIs, as well as anti-CD38 targeting monoclonal antibodies, which have led to a significant increase in response rate as well as survival rate (Dimopoulos et al, 2016; Palumbo et al, 2016; Kumar et al, 2012). While treatment for multiple myeloma will often induce remission, multiple myeloma is characterized by a recurring pattern of remission and relapse. With each subsequent line of treatment, the duration and depth of response decreases (Cook et al, 2018), and patients eventually develop treatment resistance (Papadas et al, 2017). It is not uncommon for patients to be treated with 3 or more lines of therapy.

The goal of treatment for RRMM is to achieve the longest progression-free survival (PFS) and subsequently overall survival (OS). The depth of response is associated with OS and a critical factor to achieving that goal (Chanan-Khan and Giralt, 2010; Richardson et al, 2007). Additional goals include controlling disease to prevent or delay associated complications (such as bone fractures, renal insufficiency, and infections), maintaining an acceptable health related quality of life, and providing relief of pain and other disease-related symptoms. Investigational agents that utilize both novel targets and mechanisms of action, especially those that have shown clinical activity in first-in-human studies, have the potential to achieve these goals, particularly in patients with a high unmet need after their disease has progressed following treatment with available standard-of-care therapies.

3.3.2 Key Benefits

As AMG 420 is still in early development and clinical experience is still limited, key benefits are still being investigated and will be described when the data become available.

3.3.3 Key Risks

The target cell populations of AMG 420 are plasma cells, mature and activated B-cells shown to express BCMA; hence the potential on-target toxicity is depletion of these hematologic cell types and immunoglobulin level, which could result in an increased risk of infection.

At this time, there is limited clinical experience with AMG 420 in humans. Based on biological possibility, nonclinical toxicity studies of AMG 420, and clinical safety experience with AMG 420 and other BiTE® antibody constructs in hematology, such as

blinatumomab, the safety risks for AMG 420 include cytokine release syndrome (CRS), infections, and neurologic events (see Table 3-1).

Table 3-1. Key Safety Risks for AMG 420

Safety Risk	Description
Important Identified Risks	
Cytokine Release Syndrome (CRS)	Cytokine release syndrome (CRS), including serious events, has been reported for patients receiving AMG 420 in the clinical trial setting. Signs and symptoms many include the following: • Constitutional – fever, rigors, fatigue, malaise • Neurologic – headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure • Respiratory – dyspnea, tachypnea, hypoxemia • Cardiovascular – tachycardia, hypotension • Gastrointestinal – nausea, vomiting, transaminitis, hyperbilirubinemia • Hematology – bleeding, hypofibrinogenemia, elevated D-dimer • Skin – rash
Important Potential Risks	
Infections	Infections, including device-/catheter-related infections, have been reported in the clinical trial setting with administration of AMG 420.
Neurologic Events	Neurologic events, including headache and peripheral neuropathy, have been reported in the clinical trial setting with administration of AMG 420.

Clinical signs and symptoms of CRS, infections, and neurologic events, along with other safety labs, will be monitored during the study and at the appropriate time points to ensure subjects' safety. Refer to Section 7.4.2.1.2 for specific recommendations regarding the mitigation and management of CRS, infections, and neurologic events.

Please refer to the AMG 420 Investigator's Brochure for further description of the key safety risks.

3.3.3.1 Risks

Refer to the AMG 420 Investigator's Brochure for further description of safety risks.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Phase 1b	
Primary	
• Establish the safety and tolerability of AMG 420 at dose levels of 400 μg/day and 600 μg/day in subjects with relapsed and/or refractory multiple myeloma (RRMM)	• Dose-limiting toxicities (DLTs), treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
Key Secondary	
• Estimate overall response rate (ORR) and duration of response (DOR) of AMG 420 in subjects with RRMM	• ORR • DOR
• Evaluate the rate of minimal residual disease (MRD)-negativity at the time of CR	• MRD negativity at the time of CR
Secondary	
• Establish the safety and tolerability of AMG 420 in subjects with extramedullary relapsed multiple myeloma	• DLTs, treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, ECGs, and clinical laboratory tests
• Characterize the pharmacokinetics (PK) of AMG 420 when administered as 4-week continuous intravenous (cIV) infusion	• AMG 420 PK parameters including, but not limited to, half-life ($t_{1/2}$), clearance, and apparent C_{ss}

Objectives	Endpoints
Secondary	
• Evaluate other measures of anti-myeloma activity of AMG 420 in subjects with RRMM: – Time to response – Progression-free survival (PFS) – Overall survival (OS) – Best overall response (BOR)	• Efficacy parameters according to International Myeloma Working Group (IMWG) response criteria, per investigator assessment: – Time to response – PFS – OS – BOR

Objectives	Endpoints
Exploratory	
[redacted]	

4.2 Hypotheses

A safe and tolerable dose of AMG 420 will have evidence of anti-tumor activity in patients with relapsed and/or refractory multiple myeloma as measured by the rate of overall response.

The ORR according to IMWG response criteria along with 95% CI will be calculated per investigator assessment for subjects with RRMM. The lower bound of the binomial 2-sided 95% confidence interval for ORR not lower than 35% is considered clinically meaningful.

5. Study Design

5.1 Overall Design

This is a phase 1b, multicenter, non-randomized, open-label expansion study. AMG 420 will be evaluated in adult subjects with RRMM.

The study will consist of up to a 21-day screening, a treatment period, safety follow-up (SFU), and long-term follow-up (LTFU) period. In the treatment period, treatment will be continued until PD or relapse as defined by IMWG response criteria (see Section 12.8), unacceptable safety events, next anti-multiple myeloma treatment, or other reason for permanent treatment discontinuation. All subjects will be assessed for anti-myeloma activity according to the IMWG response criteria. An SFU visit will be conducted 30 (+3) days after last administration of AMG 420, and an LTFU period will begin after the SFU visit is completed. The total duration of the LTFU will be up to 5 years from the first dose of AMG 420, or until subject death, whichever is first.

5.1.1 Phase 1b (Monotherapy Dose Confirmation)

In phase 1b, approximately 10 subjects will be treated at the 400 μg/day dose (comprising cohort 1). Approximately 10 subjects will be treated at the 600 μg/day dose level (cohort 2).

The dose level review team (DLRT) will convene and review all available safety, laboratory, and PK data at the following scheduled time points:

- After at least 10 subjects in phase 1b cohort 1 (400 μg/day dose level) have had the opportunity to complete the 4-week infusion period of the first treatment cycle: On the basis of this review, the DLRT will make a recommendation regarding the initiation of phase 1b cohort 2 (600 μg/day dose level).
- After at least 3 subjects with EM relapsed disease in phase 1b cohort 1 (400 μg/day dose level) have had the opportunity to complete the 4-week infusion period of the first treatment cycle: On the basis of this review, the DLRT will make a recommendation regarding the appropriateness of continued enrollment of subjects

with EM relapsed disease in phase 1b cohort 2 (600 μg/day dose level). Please note that enrollment of subjects with EM relapsed disease in phase 1b cohort 2 will not be allowed until this safety review of the first 3 subjects with EM disease is completed by the DLRT.

- After the first 3 subjects have been dosed with AMG 420 at 600 μg/day for the full 4-week infusion cycle in phase 1b cohort 2.

In phase 1b, the safety data will be reviewed on an ongoing basis and enrollment may be terminated at any time. To further reduce the risk of overdose to ongoing and future subjects, protocol-defined enrollment holding rules will be used. These rules are based on a modified Toxicity Probability Interval (mTPI) (Ji et al, 2010) where the target TPI is a DLT probability from 20% to 33% and the overdose TPI is > 33% DLT probability. Enrollment to the ongoing dose level/schedule will be paused per the rules in Table 5-1 during enrollment into phase 1b cohorts 1 and 2.

Table 5-1. Rules for Holding Enrollment in Phase 1b

Number of Dose-limiting Toxicities	≥ 2	≥ 3	≥ 4
Number of Treated Subjects	≤ 4	≤ 6	≤ 8

If the rules for pausing enrollment are met, no further enrollment to the respective dose level/schedule will be allowed until after a careful review of all safety data by the DLRT. Additionally, enrollment will not resume until the protocol has been amended to include additional safeguards for subject safety (eg, modifications to dose level and schedule).

Subjects with EM disease will be able to enroll into cohort 2 after the safety evaluation is complete for 3 subjects with EM disease treated at 400 μg/day.

For definition of the DLT evaluation period and DLT-evaluable subject refer to Section 7.4.1. For details on the mTPI model see Section 10.3.

An investigator will review efficacy data and assess outcomes in accordance with IMWG criteria. Investigator assessments will be used for primary efficacy analysis.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 20 subjects will be enrolled in this study.

Subjects in this clinical investigation shall be referred to as “subjects.” For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

Subjects that are not DLT-evaluable may be replaced. A subject is non-DLT-evaluable if subject discontinues treatment for any reason other than a DLT prior to completing the DLT evaluation period (see Section 7.4.1 for DLT details).

5.2.2 Number of Sites

Approximately 15 investigative sites in the European Economic Area, Australia, Japan, and the US will be included in the study. Sites that do not enroll subjects within 4 months of site initiation may be closed. Additional countries or sites may be added if deemed necessary.

5.3 End of Study

5.3.1 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), whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when data for the primary endpoint of phase 1b are last collected at month 6 after the last subject is enrolled.

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

End of Study: The end of study (EOS) 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, LTFU), as applicable.

5.3.2 Study Duration for Subjects

It is anticipated that an individual subject will participate in the study for up to approximately 5 years.

This includes a screening period lasting up to 21 days, a treatment period lasting for a median of approximately 8 months, and a follow-up period lasting up to 5 years from the first dose of AMG 420.

The actual duration for individual subjects will vary depending upon tolerability of AMG 420, evidence of clinical progression, and willingness to participate in the study.

5.4 Justification for Investigational Product Dose (AMG 420)

The primary purposes in phase 1b are to 1) confirm the safety and tolerability of the 400 μg/day dose level in subjects with or without extramedullary (EM) disease and 2) establish the safety and tolerability of the 600 μg/day dose level.

The rationale for dosing in this study is based on the observations and experiences with AMG 420 in the separate FIH study conducted by BI (1351.1), which suggests that a cIV administration is safe and has the potential to induce durable remissions in patients with RRMM. This BI 1351.1 study has identified the 400 μg/day dose level as a preliminary safe and effective dose, as this dose was well tolerated in n = 3 subjects, whereas 2 of 3 subjects treated at the 800 μg/day dose experienced DLTs. The 600 μg/day dose level was not evaluated in the FIH study. Subjects may benefit from higher exposures than are achieved at the 400 μg/day dose level; thus, safety and tolerability of the 600 μg/day dose level may be evaluated in this phase 1b study. The DLRT will convene and review all available safety, laboratory, and PK data from all subjects treated in phase 1b cohort 1 at the 400 μg/day dose before recommending evaluation of the 600 μg/day dose (phase 1b cohort 2). If the DLRT recommends the 600 μg/day dose to be safe and well-tolerated after reviewing the phase 1b cohort 2 data, the sponsor may propose changing the recommended phase 2 dose be 600 μg/day on the basis of interim data analyses.

5.5 Patient Input on Study Design

Subject input was not obtained for this study.

6. Study Population

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

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 12.3).

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

6.1 Inclusion Criteria

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

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

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

103 Multiple myeloma meeting the following criteria:

- Pathologically-documented diagnosis of multiple myeloma that is relapsed or is refractory (see Section 12.9) as defined by the following:
  - Relapsed after ≥ 3 lines of prior therapy that must include a PI, an IMiD, and a CD38-directed antibody in any order during the course of treatment OR refractory to PI, IMiD, and CD38-directed antibody.
- Measurable disease, defined by 1 or more of the following at time of screening:
  - serum M-protein ≥ 0.5 g/dL measured by serum protein electrophoresis (SPEP)
  - urinary M-protein excretion ≥ 200 mg/24 hours
  - Involved sFLC measurement > 10 mg/dL, provided that the sFLC ratio is abnormal as per IMWG response criteria

104 Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2

105 Life expectancy of at least 3 months as per investigator`s judgment at time of screening

106 Hematological function without transfusion support (within 7 days from screening assessment) as follows:

- ANC ≥ 1.0 x 10^9/L (without growth factor support)
- platelet count ≥ 50 x 10^9/L (without transfusions), but ≥ 25 x 10^9/L if the marrow is replaced by ≥ 50% myeloma (unless receiving anticoagulation therapy then platelet count must be > 50 x 10^9/L)
- hemoglobin ≥ 7.0 g/dL (transfusions permitted no later than 48 hours before screening)

107 Renal function as follows:

- calculated or measured creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation or via 24-hour urine collection with plasma and urine creatinine concentrations, respectively

108 Hepatic function as follows:

- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x upper limit of normal (ULN)
- total bilirubin (TBIL) < 1.5 x ULN (unless considered due to Gilbert's syndrome)

6.2 Exclusion Criteria

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

Disease Related

201 Known central nervous system involvement by multiple myeloma

202 Evidence of primary or secondary plasma cell leukemia at the time of screening

203 Waldenstrom's macroglobulinemia

204 Unresolved toxicities from prior anticancer therapy, defined as not having resolved to CTCAE version 5.0 grade 1 or to levels dictated in the eligibility criteria with the exception of grade 2 peripheral neuropathy, alopecia, or toxicities from prior anticancer therapy that are considered irreversible (defined as having been present and stable for > 4 weeks) which may be allowed if they are not otherwise described in the exclusion criteria and there is agreement to allow by both the investigator and Amgen medical monitor

Other Medical Conditions

205 History of other malignancy within the past 3 years, with the following exceptions:

- malignancy treated with curative intent and with no known active disease present for ≥ 1 year 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
- breast ductal carcinoma in situ with full surgical resection (ie, negative margins) and without evidence of disease
- prostate cancer with a Gleason score equal to 6 with undetectable prostate specific antigen (PSA) over 12 months
- treated medullary or papillary thyroid cancer
- adequately-treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- similar neoplastic conditions with an expectation of > 95% five-year disease-free survival
- see exclusion criterion 202 for exclusion of subjects with evidence of primary or secondary plasma cell leukemia at the time of screening

206 Known history of amyloidosis

207 Current or known history of autoimmune diseases requiring systemic treatment in past 5 years except vitiligo, resolved childhood asthma/atopy, or subjects with history of hypothyroidism after completing treatment for autoimmune thyroid disease, stable on hormone replacement therapy.

208 Clinically not-controlled chronic or ongoing infectious disease requiring treatment at the time of study day 1 or within the 14 days before study day 1

209 Symptomatic peripheral sensory or motor neuropathy of grade ≥ 3

210 History or presence of clinically relevant central nervous system (CNS) pathology as uncontrolled epilepsy or seizure disorder, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, and psychosis

211 Active hepatitis B and C based on the following results:

- Positive for hepatitis B surface antigen (HepBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B)

- Negative HepBsAg and positive for hepatitis B core antibody: Negative hepatitis B virus DNA by polymerase chain reaction (PCR) result is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B.
- Positive Hepatitis C virus antibody (HepCAb): Negative hepatitis C virus RNA by PCR result is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C

212 Known or suspected HIV infection or subjects who are HIV seropositive

213 Baseline ECG QTc > 470 msec (applying Fridericia correction), defined as the average of individual baseline ECGs

Prior/Concomitant Therapy

214 Previously received an allogeneic stem cell transplant and the occurrence of 1 or more of the following:

- received the transplant within 6 months prior to study day 1
- received immunosuppressive therapy within the last 3 months prior to study day 1
- any active acute graft versus host disease (GvHD), grade 2 to 4, according to the Glucksberg criteria or active chronic GvHD requiring systemic treatment
- any systemic therapy against GvHD within 2 weeks prior to start of investigational product treatment

215 Autologous stem cell transplantation < 90 days prior to study day 1

216 Treatment with systemic immune modulators including, but not limited to, nontopical systemic corticosteroids (unless the dose is ≤ 10 mg/day prednisone or equivalent), cyclosporine, and tacrolimus within 2 weeks before study day 1

217 Last anticancer treatment (chemotherapy, IMiD, PI, molecular targeted therapy) < 2 weeks prior to study day 1

218 Last treatment with a therapeutic antibody less than 4 weeks prior to study day 1

219 Radiation therapy to multiple anatomic sites within 28 days prior to study day 1. Focal radiotherapy within 14 days prior to study day 1.

220 Major surgery defined as surgery requiring general anesthesia with endotracheal intubation within 28 days prior to study day 1, unless discussed with and eligibility approved by Amgen medical monitor

221 Prior treatment with any drug that specifically targets BCMA on tumor cells (eg, other bi-specific antibody constructs, antibody drug conjugates, or CAR T-cells, except for subjects who were previously treated with AMG 420 in this study.

222 Treatment with medications known to cause QTc interval prolongation within the washout periods described in Section 12.10 unless approved by the Amgen medical monitor

Prior/Concurrent Clinical Study Experience

223 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Other Exclusions

224 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 6 weeks after the last dose of investigational product.

225 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 6 weeks after the last dose of investigational product. Refer to Section 12.5 for additional contraceptive information.

226 Female subjects with a positive pregnancy test assessed at screening or within 7 days prior to enrollment (unless a confirmatory serum pregnancy test is negative after a positive urine result).

227 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 14 weeks after the last dose of investigational product. Refer to Section 12.5 for additional contraceptive information.

228 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional 14 weeks after the last dose of investigational product.

229 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 14 weeks after the last dose of investigational product.

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

231 Subjects likely to not be available to complete all protocol-required study visits or procedures, including BM aspirates/biopsies, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.

232 History or evidence of any other clinically-significant disorder, condition, or disease (eg, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia requiring therapy at time of screening) with the exception of those outlined above that, in the opinion of the investigator or Amgen medical monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

6.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 12.3).

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 along with the lab results and any requested supporting documentation for review of eligibility criteria. The completed Eligibility Worksheet should be 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 subject's eligibility.

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

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

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by Interactive Response Technology (IRT). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The unique subject identification number will consist of 11 digits. The first 3 digits will represent the last 3 digits of the protocol number (ie, 370). The next 5 digits will represent the country code and site number (eg, 26001) and will be identical for all subjects at the site. The next 3 digits will be assigned in sequential order as subjects are screened (eg, 001, 002, or 003). For example, the first subject to enter screening at site 26001 will receive the number 37026001001, and the second subject at the same site will receive the number 37026001002.

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

Enrollment in the study will begin with cohort 1. An Amgen representative will notify the site in writing when cohort 2 is open to screen and enroll subjects. Sites will also be informed as to which cohort their subjects will be allocated to by the Sponsor.

6.4 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, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a maximum of 2 times. Refer to Section 9.1.1.

7. Treatments

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

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

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Section 7.1 below.

7.1 Treatment Procedures

7.1.1 Investigational Product: AMG 420

7.1.1.1 AMG 420 Dosage Formulation

AMG 420 is manufactured by Boehringer Ingelheim Pharma GmbH & Co. KG, packaged by Amgen Inc., and distributed using Amgen clinical study drug distribution procedures.

AMG 420 is supplied as a sterile, preservative-free lyophilized powder for IV administration after reconstitution with sterile Water for Injection (WFI). The final container is a single-use, 4 mL glass vial and contains a target extractable amount of 75 μg AMG 420.

The intravenous solution stabilizer (IVSS) is supplied as a sterile solution in a 10 cc glass vial containing 10 mL deliverable product. The IVSS does not contain an active pharmaceutical ingredient. The IVSS is intended for pretreatment of the IV bags prior to dilution of AMG 420 drug product.

Refer to the IPIM for further details.

7.1.1.2 AMG 420 Dosage, Administration, and Schedule

AMG 420 will be administered as a cIV infusion. A treatment cycle consists of a 4-week infusion period followed by a 2-week infusion-free interval prior to the following treatment cycle (phase 1b, monotherapy). Refer to Section 7.4.2.1.2.2 for treatment delays due to AEs.

Cohort 1

Subjects in cohort 1 will receive a dose of 400 μg/day starting on day 1 of each treatment cycle. If a dose step is determined to be needed after DLRT review of all

available safety data, the initial dose will be 200 µg/day for the first 3 days of treatment cycle 1. On day 4 of cycle 1 and for the remainder of cycle 1, the dose for cohort 1 will then be escalated (dose step) to 400 µg/day. From cycle 2 onwards, the dose will remain at 400 µg/day, no dose step will be required.

Cohort 2

Subjects in cohort 2 will receive a dose of 200 µg/day for the first 3 days of treatment cycle 1. On day 4 of cycle 1 and for the remainder of cycle 1, the dose for cohort 2 will then be escalated (dose step) to 600 µg/day. From cycle 2 onwards, the dose will remain at 600 µg/day and no dose step will be required. See Section 12.11 for procedures.

Subjects with EM disease will be able to enroll into cohort 2 after the safety evaluation is complete for 3 subjects with EM disease treated at 400 µg/day (cohort 1).

7.1.1.3 MRD-based Extended Treatment-free Interval

The **treatment**-free interval may be increased as follows:

- Up to 4 weeks in subjects who attain MRD-negative disease status at 6 months from enrollment (based on all appropriate assessments to fulfill IMWG criteria),
- Up to 8 weeks in subjects who remain in MRD-negative disease status at 12 months from enrollment. Treatment will continue until progression or at the discretion of the investigator, can be discontinued at 24 months if subjects remains in complete remission.

The treatment free interval may be decreased to the initial treatment free interval of 2 weeks at the discretion of the investigator upon informing the sponsor. Reinstatement of the treatment free interval at the cadence prior to the decrease is not permitted.

7.1.1.4 Dosing Instructions

The Amgen investigational product (AMG 420) 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 (AMG 420) is started for immediate intervention in case of complications.

AMG 420 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 420 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines.

The drug will be administered as a cIV infusion at a constant flow rate.

The drug should not be administered as a bolus and flushing residual drug at the time of bag change is prohibited. The final solution for infusion should be administered through a sterile 0.2 µm in-line filter.

Infusion bags should be changed in accordance with country regulations and local pharmacy standards for infusion of compounded sterile products up to 48 hours in the US and up to 96 hours in Australia and Europe.

The start time of infusion should be chosen carefully to avoid any interference or inconvenience with time points of safety assessments, PK/pharmacodynamic measurements, and infusion bag changes.

Any infusion interruption that is longer than 1 hour should be recorded on the eCRF (including start date/time and stop date/time) with the exception of adverse events. Any infusion interruption due to an adverse event, independent of the duration of the interruption, should be recorded on the eCRF.

Details for handling infusion interruptions are outlined in Section 7.4.2.

7.1.1.4.1 AMG 420 Inpatient Dosing/Hospitalization

Minimum hospitalization times for subjects will be as follows:

- Cycle 1: 48 hours or 6 days after start of infusion if step dosing is utilized.
- Cycle 2: 24 hours monitoring after start of infusion; longer monitoring can be decided upon at investigator's discretion.
- Cycles 3 and 4: 4 hours monitoring after start of infusion.
- Cycle 5 and subsequent cycles: hospitalization not required unless subject experiences an adverse event requiring hospitalization as indicated in Section 2.2 of the study protocol or if clinically indicated. The length of hospitalization required in these cases is to be determined by the investigator.
- Re-start of treatment after an interruption due to adverse event: 48 hours.
- Re-start of treatment after an interruption of $>$ 4 hours due to technical/logistical issue: 24 hours.
- Any cycle with dose re-escalation: 48 hours after dose re-escalation.

For cycles 1 and 2 in-hospital administration, study sites must have immediate access to a medical intensive care unit staffed by critical care providers. Prior to hospital discharge, vital signs will be measured in order to detect possible signs and symptoms of infusion reactions or CRS. If required for logistical reasons (eg, long travel times),

subjects may be hospitalized the day before start of dosing (day -1) of any cycle, as well as at the end of infusion (EOI) for cycle 1 for required PK samples.

7.1.1.4.2 AMG 420 Outpatient Dosing

If deemed stable by the investigator, a subject may continue AMG 420 cIV infusion as an outpatient.

For infusion bag changes in the outpatient setting, the subject will either return to the study site or be visited by a well-trained home health care service (HHCS) provider at the required frequency. If home visits for IV bag changes are required, the HHCS provider will change the infusion bag, measure vital signs, monitor, document and report adverse events/serious adverse events per Section 9.2.3, and document any issues with the cIV infusion or infusion pump. The subject and HHCS provider will be trained and will receive written instructions for storage of the IV bags, if applicable. The HHCS provider will complete the study delegation log and will be authorized by the investigator before any study-related tasks are started.

Refer to the home health care manual for detailed information on the storage, handling, and administration of AMG 420, mandatory procedures, and data collection requirements.

Following each visit or telephone contact by the HHCS provider, the information collected will be documented on the HHCS's visit worksheet and forwarded to the investigator. Any unexpected or unusual events, as well as deviations will be communicated promptly to the investigator. If any adverse event/serious adverse event occurs in the outpatient setting, the HHCS provider should directly contact the site for further management. The HHCS professionals provide 24-hour emergency on-call service for any pump related issues. In the event of an infusion interruption of the AMG 420 cIV infusion management of the interruption and re-start of the infusion should be performed as outlined in Section 7.4.2.

7.1.1.5 Drug Accountability

The planned dose, start date, start time, stop date, stop time, dose administered, reason for dose change, and package lot number of AMG 420 are to be recorded on each subject's eCRF(s) and the site's study files.

7.1.2 Non-investigational Products

This study will not use non-investigational products.

7.1.3 Medical Devices

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

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

Amgen investigational product (AMG 420) 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 both the inpatient and outpatient setting. Investigational product solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines with a 0.2 μm in-line filter that are both compatible with the investigational product. 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.

7.1.4 Other Protocol-required Therapies

All other protocol-required therapies including, glucocorticoids and tocilizumab, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

7.1.4.1 Glucocorticoid Premedication

Premedication with IV glucocorticoids, as described below, is required. Administration of glucocorticoids is recommended to occur 30 to 60 minutes before the start of AMG 420 treatment cycles and must not occur earlier than 2 hours, to prevent/reduce severity of infusion-related reactions and CRS.

- prior to cycles 1 and 2, as well as prior to dose step in cycle 1: equivalent to 50 mg prednisone, 40 mg methylprednisone, or 8 mg dexamethasone
- prior to cycle 3: equivalent to 25 mg prednisone, 20 mg methylprednisone, or 4 mg dexamethasone

If AMG 420 is tolerated well, the investigator may decide to further reduce or do without premedication in later treatment cycles.

Premedication will also be required 30 to 60 minutes before re-start of the infusion in case of an infusion interruption for > 1 week. The premedication dose will be the same that was administered prior to start of the cycle unless adjustments are needed based on investigator judgement.

7.1.4.2 CRS Treatment

For administration of dexamethasone or tocilizumab after occurrence of CRS, follow guidance in Table 7-3. In advance of AMG 420 administration and possible CRS that may warrant the administration of tocilizumab for CRS, evaluate subjects for tuberculosis risk factors and identify those at risk for reactivation via notation in the medical record. For subjects with a past medical history of latent or active tuberculosis or positive test for latent tuberculosis at screening, tocilizumab should be administered according to warning and precautions guidelines for tuberculosis provided in the tocilizumab regional prescribing information. All sites will ensure that CRS rescue medications are available on-site, including corticosteroids and (for sites in regions where tocilizumab is approved and available, eg, the US and Germany) 2 doses of tocilizumab per study subject.

7.1.5 Other Treatment Procedures

No other treatment procedures are applicable in this study.

7.1.6 Product Complaints

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

This includes any investigational product (AMG 420) provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with an investigational product (AMG 420) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

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

The following treatments and/or procedures are excluded during the treatment period of the study (until SFU):

- any antitumor therapy other than AMG 420, such as:
  - cytotoxic and/or cytostatic drugs
  - radiation therapy (with the exception of radiotherapy for palliative care such as bone pain; this is only permitted after discussion with Amgen medical monitor)
  - immunotherapy

- any other immunosuppressive therapies (except for the management of acute, treatment-related toxicities such as transient - ie, for up to 2 weeks - use of corticosteroids and tocilizumab)
  - high-dose corticosteroid therapy (dexamethasone > 24 mg/day or equivalent) is only allowed for up to 7 days
- any other investigational agent
- treatment with medications known to cause QTc interval prolongation unless approved by the Amgen medical team (see Section 12.10)
- any major surgery, except for surgery for palliative repair of pathologic fractures, as long as determined not to be due to disease progression
- none of the medications mentioned in Section 7.8.2 are excluded during the study

7.1.8 Vaccines

The use of vaccines except live and live-attenuated vaccines will be allowed during therapy per regional and institutional standard of care. Throughout the trial, SARS-COV-2 vaccination should be avoided within 3 days after the administration of AMG 420. In the event where a patient requires steroids for treatment of AEs, vaccination should be avoided while on steroids.

7.2 Method of Treatment Assignment

An Amgen representative will notify the site(s) in writing when a cohort or study part, respectively, are open to screen and enroll subjects.

Subjects who meet eligibility criteria will be assigned to treatment with AMG 420.

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

7.3 Blinding

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

7.4 Dose Modification

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

The DLT evaluation period (ie, DLT-evaluable period) will be the 4 weeks on AMG 420 treatment within the first treatment cycle, starting on day 1 (start of infusion). The DLT evaluation period may also be extended to assess events starting within the window in case the DLT definition is time dependent.

Treatment in AMG 420 cycle 1 will be considered complete and the subject will be DLT evaluable if the subject has completed the DLT evaluation period or experienced a DLT any time during the DLT evaluation period. A subject will be non-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 non-DLT-evaluable will still be evaluated and considered in DLRT decisions (see also Section 10.4.1.1.1.1).

See Section 5.2.1 for description of replacement of subjects.

A DLT will be defined as any of the events described below occurring in a subject during the DLT evaluation period unless clearly attributable to causes other than treatment with AMG 420. The CTCAE version 5.0 (see Section 12.4) will be used to assess toxicities/adverse events with the exception of CRS and TLS (see Section 7.4.2.1.2.5 and Section 12.12 for grading criteria of CRS and TLS, respectively).

- Death not clearly due to the underlying disease or extraneous causes.

Non-hematologic DLTs:

- Non-hematological adverse event grade 3 or higher, EXCEPT:
  - infection responding to antibiotic/anti-infective treatment within 48 hours
  - grade 3 fatigue or asthenia
  - grade 3 headache resolving to ≤ grade 2 within 72 hours
  - grade 3 insomnia resolving to ≤ grade 2 within 7 days
  - grade 3 fever resolving to ≤ grade 2 within 72 hours
  - grade 3 nausea, vomiting, or diarrhea responding if successfully managed with optimal medical support and resolved within 72 hours
  - laboratory parameters of grade ≥ 3, not considered clinically relevant, and improved to grade ≤ 2 within 72 hours
- Any subject meeting the criteria for Hy's Law case (ie, severe drug-induced liver injury [DILI]) will be considered a DLT. A Hy's Law case is defined as: AST or ALT values of ≥ 3 x ULN AND with serum TBIL level of > 2 x ULN or international normalized ratio (INR) > 1.5 without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities (see Section 7.4.3 for hepatotoxicity management and Section 12.7 for further explanation of Hy's law case and management of hepatic function).

Hematologic DLTs:

- febrile neutropenia grade 4
- febrile neutropenia grade 3 unless responding to antibiotic/anti-infective treatment within 48 hours
- grade 4 neutropenia lasting more than 5 days, grade 4 thrombocytopenia lasting more than 7 days, grade 3 thrombocytopenia with hemorrhage or required platelet transfusion, or grade 4 anemia in the absence of detectable multiple myeloma as it may reflect a marrow toxic effect of AMG 420

The dosing schedule is described in the Schedule of Activities (Section 2.2).

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

7.4.2.1 Amgen Investigational Product: AMG 420

The reason for dose change of AMG 420 is to be recorded on each subject's eCRF(s).

7.4.2.1.1 Infusion Interruptions and Re-Start in Case of Technical/Logistical Issues

The administration of AMG 420 should not be interrupted, if possible. In case of infusion interruption due to any technical or logistical reason (eg, a technical problem with the infusion pump, diagnostic measurements, or the investigational product is incorrectly prepared or administered), the interruption should be as short as possible, and the infusion continued at the earliest time possible.

If the interruption is longer than 4 hours, re-start of the infusion should be performed in the hospital, under the supervision of the investigator. If the interruption occurs during cycles 1 or 2, the subject should be observed for 24 hours after re-start for possible side effects. If the interruption occurs in cycle 3 or beyond, the subject should be observed for 4 hours. Premedication as described in Section 7.1.4 must be administered prior to resumption of AMG 420 infusion, if applicable.

The assessments that should be performed prior to re-start of infusion as for cycle 1 days 1 and 2 are specified in the Schedule of Activities (see Section 2.2).

Every interruption longer than 1 hour should be documented on the eCRF.

7.4.2.1.2 Infusion Interruptions/Re-Start/Dosage Adjustments due to Adverse Events

7.4.2.1.2.1 General Guidelines

Subjects should be assessed for adverse events at each visit. The severity of the adverse event will be graded using the CTCAE version 5.0 (Section 12.4), with the exception of CRS, which must be graded using the criteria referenced in the publication by Lee et al, 2014 (see Table 7-3) and TLS, which must be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al, 2008 (see Section 12.12).

Infusion modification and dose reduction due to an adverse event will be performed according to the instructions described below and outlined in Table 7-1 and Table 7-3.

Infusion interruptions for other reasons need to be discussed with the Amgen medical monitor.

If infusion interruptions of < 14 days occur within a cycle the cycle will be resumed. The counting of the cycle days will not be stopped with an infusion interruption (eg, if the infusion is stopped on cycle day 5 and resumed 5 days later, the day of re-start is cycle day 10).

Following an infusion interruption with < 7 days remaining for infusion after resumption of the cycle, the last treatment days can be skipped and treatment will be continued with the next cycle after a 2-week infusion free interval.

However, treatment should not be given for < 14 days per cycle. An infusion interruption of more than 2 weeks or several interruptions exceeding a total of 14 days of treatment per cycle due to serious adverse events/adverse events require permanent treatment discontinuation.

Please note: the guidance in Section 7.4.2.1.2 does not apply to the treatment holiday described in Section 7.1.1.2.

7.4.2.1.2.2 Infusion Interruptions Due to Adverse Events

Events occurring during the 4-week infusion period of a treatment cycle and requiring treatment interruption will be managed by infusion interruption.

Any treatment interruption due to an adverse event, independent of the duration of the interruption, should be documented on the eCRF including start and stop date/time of the infusion.

Delay of Subsequent Infusion due to Adverse Events

Events occurring after the end of the infusion and requiring a delay of treatment will be managed by delay of the subsequent infusion. The site should record any delay of an infusion on the eCRF and provide the start and stop date/time of the infusion.

Events requiring a delay of the subsequent infusion are listed in Table 7-1. Infusion interruptions or delays **greater than 7 days** for other reasons need to be discussed with the Amgen Medical Monitor. **Delays of treatment cycles beyond 14 days are not permitted.**

Events requiring an infusion interruption including guidance for management, re-start, and permanent discontinuation are listed in Table 7-1 and Table 7-3.

7.4.2.1.2.3 Re-Start of Infusion

Re-starting treatment after interruption due to an adverse event should be performed in the hospital under medical supervision. Premedication as described in Section 7.1.4 must be administered prior to re-start, if applicable.

The assessments that should be performed as for cycle 1 days 1, 2, and 3 are specified in the Schedule of Activities (see Section 2.2):

The subject should be hospitalized for at least 48 hours after re-start of the infusion (see also Section 7.1.1.4.1).

7.4.2.1.2.4 Dosage Adjustments/Re-Start at a Lower Dose Level/ Dose-Escalation

For adverse events for which re-start of treatment is allowed according to the guidelines outlined in Table 7-1 and Table 7-3, treatment may be resumed under medical supervision at the same dose or a lower dose.

Premedication as described in Section 7.1.4 must be administered prior to re-start, if applicable.

Re-start at a lower dose level:

If clinically indicated per the guidance provided in Table 7-1 and Table 7-3, treatment will be resumed at a lower dose level (ie, 200 μg/day for subjects originally receiving 400 μg/day or 400 μg/day for those originally receiving 600 μg/day) and continued until the pre-scheduled end of the cycle.

The assessments that should be performed as for cycle 1 days 1, 2, and 3 are specified in the Schedule of Activities (see Section 2.2).

The subject should be hospitalized for at least 48 hours after re-start of the infusion (see also Section 7.1.1.4.1).

Only one dose de-escalation step per subject is allowed in the study. In case an additional dose de-escalation is required for a subject, permanently discontinue treatment.

Dose-escalation:

Dose-escalation is allowed with start of the next treatment cycle if treatment is well tolerated and escalation is appropriate according to the investigator's judgement. In addition to the assessments required as per Schedule of Activities (see Section 2.2), a

neurological examination should be performed before dosing in case the infusion interruption was due to a neurologic event.

The subject should be hospitalized for at least 48 hours after dose-escalation (see also Section 7.1.1.4.1).

Table 7-1. Infusion Interruptions/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption	Specific Management	Re-Start Guidance	Permanent Discontinuation
Infusion-related Reaction				
Grade 1	n/a	• Consider supportive medication according to local standard of care. • Increase monitoring of vital signs as medically indicated.	Continue infusion	n/a
Grade 2	Immediate interruption until event has improved to grade ≤ 1		• Resume infusion at half the previous rate when symptoms have resolved for at least 30 minutes, observe patient and re-escalate to basal rate after 60 minutes if successfully managed and improvement to grade ≤ 1 in ≤ 14 days. • Hospitalization: 48 hours for start of next infusion • Dose modification: resume at the same dose OR consider reducing to next lower dose if clinically indicated (ie, 200 μg/day for subjects originally receiving 400 μg/day or 400 μg/day for those originally receiving 600 μg/day) • Additional measures: additional assessments and premedication as indicated in Sections 7.4.2.1.2.3 /7.4.2.1.2.4	If interruption is > 14 days

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Table 7-1. Infusion Interruptions/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption	Specific Management	Re-Start Guidance	Permanent Discontinuation
Infusion-related Reaction (continued)				
Grade 3	Immediate interruption until event has improved to grade ≤ 1	• Consider supportive medication including steroids as clinically indicated. • Increase monitoring of vital signs as medically indicated.	• As for grade 2 infusion-related reaction, with the exception that dose modification is mandatory: reduce to next lower dose (200 μg/day for subjects originally receiving 400 μg/day or 400 μg/day for those originally receiving 600 μg/day)	If interruption is > 14 days If occurs on > 2 occasions
Grade 4	Immediate interruption	As for grade 3 infusion-related reaction	Do not restart	Permanent discontinuation
Cytokine Release Syndrome				
For Grading, Stopping and Rechallenge Rules please refer to Table 7-3				

Table 7-1. Infusion Interruptions/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption	Specific Management	Re-Start Guidance	Permanent Discontinuation
Tumor Lysis Syndrome (TLS) – Grading according to Cairo-Bishop Criteria				
Grade2 - 3	Immediate interruption until event has improved to grade ≤ 1	TLS prevention and management as per local standard of care and institutional guidelines.	• Re-start possible if successfully managed and improvement to grade ≤ 1 in ≤ 14 days • Hospitalization: Minimum 48 hours for start of next infusion • Dose modification: reduce to next lower dose (ie, 200 μg/day for subjects originally receiving 400 μg/day or 400 μg/day for those originally receiving 600 μg/day) or if dose escalation is desired consult with Amgen medical monitor. Additional measures: additional assessments and TLS premedication prior to infusion restart and next cycle infusion as per institutional standards Sections 7.4.2.1.2.3/7.4.2.1.2.4	If symptoms/signs do not resolve in ≤ 14 days, consult with Amgen medical monitor if restarting treatment is desired. In case of appearance of same event at grade 3 or higher.
Grade 4	Immediate interruption	As for grade 3 TLS	• Do not restart	Permanent discontinuation

Table 7-1. Infusion Interruptions/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption	Specific Management	Re-Start Guidance	Permanent Discontinuation
Neurotoxicity				
≥ Grade 3 OR if increased from grade 0 to grade 2	Immediate interruption	Neurological examination should be performed before resuming dosing in case the infusion interruption was due to a neurologic event.	• Re-start possible if successfully managed and improvement to ≤ grade 1 or baseline in ≤ 14 days (up to 28 days if approved by medical monitor) • Hospitalization: 48 hours • Dose modification: resume at lower dose (200 μg/day) • Additional measures: additional assessments and premedication as indicated in Sections 7.4.2.1.2.3/7.4.2.1.2.4	• If interruption is > 28 days • Grade 3 event leading to treatment interruption and has not resolved to ≤ grade 1 within 14 days despite infusion interruption • Grade 3 event that recurs after dose reduction • Grade 4 event
Hepatotoxicity				
For Stopping and Rechallenge Rules please refer to Section 7.4.3				

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Table 7-2. Additional Guidance on Infusion Interruptions/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption	Specific Management	Re-Start Guidance	Permanent Discontinuation
Any other AMG 420 related events not meeting dose-limiting toxicity (DLT) criteria				
≥ Grade 3	Interruption required if Grade 4 event, or if Grade 3 event is deemed intolerable by the subject or investigator and not responding to appropriate medical management until event has improved to grade ≤ 2 (grade ≤ 1 in the case of neurological event)	Neurological examination should be performed before resuming dosing in case the infusion interruption was due to a neurologic event.	• Re-start possible if successfully managed and improvement to grade ≤ **2** in ≤ 14 days. • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated (ie, 200 μg/day for subjects originally receiving 400 μg/day or 400 μg/day for those originally receiving 600 μg/day) • Additional measures: additional assessments and premedication as indicated in Sections 7.4.2.1.2.3/7.4.2.1.2.4	If interruption is > 14 days In case of reappearance of same event at Grade 4

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Abbreviations and footnotes defined on last page of table.

Table 7-2. Additional Guidance on Infusion Interruptions/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption	Specific Management	Re-Start Guidance	Permanent Discontinuation
Any Non-AMG 420 related events				
Grade 4	Interruption required if Grade 4 event, or if Grade 3 event is deemed intolerable by the subject or investigator and not responding to appropriate medical management until event has improved to Grade ≤ 2	n/a	• Re-start possible if successfully managed and improvement to grade ≤ **2** in ≤ 14 days. • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated (ie, 200 μg/day for subjects originally receiving 400 μg/day or 400 μg/day for those originally receiving 600 μg/day) • Additional measures: additional assessments and premedication as indicated in Sections 7.4.2.1.2.3/7.4.2.1.2.4	If interruption is > 14 days In case of reappearance of same event at Grade 4

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Abbreviations and footnotes defined on last page of table.

Table 7-2. Additional Guidance on Infusion Interruptions/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption	Specific Management	Re-Start Guidance	Permanent Discontinuation
SARS-CoV-2 infection and COVID19 disease				
asymptomatic	**Interruption required until at least 10 days since positive SARS-COV-2 test UNLESS patient previously fully vaccinated against SARS-COV-2. If patient previously vaccinated and tests positive, then discuss with Medical Monitor.**	**Follow local guidelines and standard of care for COVID-19 treatment and isolation** **Contact Amgen Medical Monitor within 1 business day to ensure appropriate documentation & management of study activities.**	• **Re-start possible upon agreement between Investigator and Amgen Medical Monitor provided:** ○ **There are no new findings on physical exam related to SARS-COV-2, AND** ○ **Subject tests negative for SARS-COV-2 by RT-PCR** **OR** ○ **If subject continues to test positive for SARS-COV-2 more than 10 days after initial positive test, or If subject initially tests positive in the setting of prior COVID vaccination, resume IP only after discussion with patient and reassessment of individual risk/benefit** • **Consider chest imaging, ECG, ECHO, and cardiology assessment 1** • **Consider hospitalization for re-start of IP based on length of treatment interruption, risk of CRS at restart, and amount of time since patient was last treated 2** • **Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated** • **Premedication and assessments: follow guidance in SOA tables**	**Immediately stop the infusion (if applicable) and permanently discontinue IP therapy IF:** **Subject required treatment interruption greater than 28 days and upon discussion with Amgen Medical Monitor the decision is made to permanently discontinue treatment** **OR** **Initial benefit/risk assessment for individual patient is not maintained any longer**

Abbreviations and footnotes defined on last page of table.

Table 7-2. Additional Guidance on Infusion Interruptions/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption	Specific Management	Re-Start Guidance	Permanent Discontinuation
SARS-CoV2 infection and COVID19 disease				
symptomatic	**Interruption required until at least 10 days since complete resolution of acute symptoms**	**Follow local guidelines and standard of care for COVID-19 treatment and isolation** **Contact Amgen Medical Monitor within 1 business day to ensure appropriate documentation & management of study activities.**	• **Re-start possible upon agreement between Investigator and Amgen Medical Monitor provided:** ○ **There are no new findings on physical exam and chest imaging, related to SARS-COV-2** ○ **Subject tests negative for SARS-COV-2 by RT-PCR** **OR** ○ **If subject continues to test positive for SARS-COV-2 more than 10 days after initial positive test, resume IP only after discussion with patient and reassessment of individual risk/benefit** • **Consider chest imaging, ECG, ECHO, and cardiology assessment 1** • **Consider hospitalization for re-start of IP based on length of treatment interruption, risk of CRS at restart, and amount of time since patient was last treated 2** • **Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated** • **Premedication and assessments: follow guidance in SOA tables**	**Immediately stop the infusion (if applicable) and permanently discontinue IP therapy IF** **Subject required treatment interruption greater than 28 days due to severe or life-threatening COVID-19** **OR** **Initial benefit/risk assessment for individual patient is not maintained any longer**

CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; ECHO = echocardiogram; IP = investigational product; RT-PCR = real time polymerase chain reaction; SARS-COV-2 = severe acute respiratory syndrome coronavirus 2; SOA = Schedule of Activities.

7.4.2.1.2.5 Specific Guidance for Cytokine Release Syndrome

Cytokine release syndrome is clinically defined and may have various manifestations. There are no established diagnostic criteria. Signs and symptoms of CRS may include:

- constitutional: fever, rigors, fatigue, malaise
- neurologic: headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure
- respiratory: dyspnea, tachypnea, hypoxemia
- cardiovascular: tachycardia, hypotension
- gastrointestinal: nausea, vomiting, transaminitis, hyperbilirubinemia
- hematology: bleeding, hypofibrinogenemia, elevated D-dimer
- skin: rash

Subjects may be at an increased risk for CRS during the first few days following the initial infusion of AMG 420. Cytokine release syndrome may be life-threatening or fatal. Infusion reactions may be clinically indistinguishable from manifestations of CRS. Throughout the treatment with AMG 420, monitor subjects for clinical signs (eg, fever, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to CRS.

Grading and management of CRS should be performed according to the guidelines provided in Table 7-3 (based on the adopted grading system referenced in Lee et al, 2014).

Please also refer to the general guidance for re-start of infusion after interruption due to adverse event in Section 7.4.2.1.2

For grade 3 and 4 CRS, please also see Section 7.4.1 for DLT considerations.

Table 7-3. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity[a]	Interruption	Minimum Expected Intervention	Re-Start Guidance	Permanent Discontinuation
1	Symptoms are not life-threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise	n/a	Administer symptomatic treatment (eg, paracetamol/acetaminophen for fever). Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution, whichever is earlier.	n/a	n/a
2	Symptoms require and respond to moderate intervention • Oxygen requirement < 40% (for room air, oxygen saturation 90% or less), OR • Hypotension responsive to fluids or low dose of 1 vasopressor, OR • Grade 2 organ toxicity or grade 3 transaminitis per CTCAE criteria	Immediately interrupt AMG 420 until event has improved to CRS grade ≤ 1, but for no less than 72 hours.	Administer: • Symptomatic treatment (eg, paracetamol/acetaminophen for fever) • Supplemental oxygen when oxygen saturation is < 90% on room air • Intravenous fluids or low dose vasopressor for hypotension when systolic blood pressure is < 85 mmHg. Persistent tachycardia (eg, > 120 bpm) may also indicate the need for intervention for hypotension. Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution to CRS grade ≤ 1, whichever is earlier. Investigators may also use tocilizumab[c] as an additional therapy in this setting at a dose of 4-8 mg/kg as a single dose, particularly if CRS does not improve to grade ≤ 1 within 4 hours after dose interruption. For subjects with extensive co-morbidities or poor performance status, manage per grade 3 CRS guidance below.	• Re-start possible, if successfully managed and improvement to CRS grade ≤ 1 within 7 days, • Consult with Amgen medical monitor first. • Hospitalization: 48 hours • In the event of 2 consecutive cases of CRS of grade 2, consider reducing dose to 200 μg/day for subjects originally receiving 400 μg/day or 400 μg/day for those originally receiving 600 μg/day • Additional measures: additional assessments and premedication as indicated in Sections 7.4.2.1.2.3/ 7.4.2.1.2.4	• If there is no improvement to CRS ≤ grade 1 within 7 days • If interruption is > 14 days • In case of repeat grade 2 event despite dose reduction

Footnotes defined on last page of table.

Table 7-3. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity[a]	Interruption	Minimum Expected Intervention	Re-Start Guidance	Permanent Discontinuation
3	Symptoms require and respond to aggressive intervention • Oxygen requirement ≥ 40%, OR • Hypotension requiring high dose[b] or multiple vasopressors, OR • Grade 3 organ toxicity or grade 4 transaminitis per CTCAE criteria	Immediately interrupt/ delay AMG 420 until event has improved to CRS grade ≤ 1.	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). The dose should then be reduced step-wise. AND/OR Investigators should also consider use of tocilizumab[c] as an additional therapy in this setting at a dose of 4-8 mg/kg as a single dose.	As for CRS grade 2	• If there is no improvement to CRS ≤ grade 2 within 5 days and CRS ≤ grade 1 within 7 days. • In case of 2 separate grade 3 CRS events. • If interruption is > 14 days
4	Life-threatening symptoms • Requirement for ventilator support OR • Grade 4 organ toxicity (excluding transaminitis) per CTCAE criteria	n/a	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). Further corticosteroid use should be discussed with the Amgen medical monitor. Additionally, tocilizumab[c] should be administered at a dose of 4-8 mg/kg as a	n/a	Immediately stop the infusion (if applicable) and permanently discontinue AMG 420 therapy.

			single dose and may be repeated once within 24 to 48 hours based on clinical assessment.		

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Footnotes defined on next page
CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous
[a] Revised grading system for cytokine release syndrome (Lee et al, 2014)
[b] High dose vasopressors (all doses are required for ≥ 3 hours): norepinephrine monotherapy ≥ 20 μg/min, dopamine monotherapy ≥ 10 μg/kg/min, phenylephrine monotherapy ≥ 200 μg/min, epinephrine monotherapy ≥ 10 μg/min; if on vasopressin, vasopressin + norepinephrine equivalent of ≥ 10 μg/min; if on combination vasopressors (not vasopressin), norepinephrine equivalent of ≥ 20 μg/min.
[c] All sites will ensure that CRS rescue medications are available on-site, including corticosteroids and (for sites in regions where tocilizumab is approved and available, eg, the US and Germany) 2 doses of tocilizumab per study subject.

7.4.2.1.3 Permanent Discontinuation of AMG 420

AMG 420 treatment will be permanently discontinued in the event of:

- infusion-related reaction grade 4 (the infusion has to be stopped immediately)
- grade 4 CRS
- grade 2 or 3 CRS meeting any of the criteria listed below:
  - grade 2 or 3 CRS that does not improve to ≤ grade 1 within 7 days
  - grade 3 CRS that does not improve to ≤ grade 2 within 5 days
  - if a subject experiences 2 separate grade 3 CRS events
  - if a subject experiences repeat grade 2 CRS event after dose reduction
  - grade 3 CRS at the initial run-in dose of the first treatment cycle if a dose step is being used
- grade 3 or higher TLS
- neurologic events considered related to AMG 420 by the investigator and meeting one or more of the following criteria:
  - grade 3 neurologic event leading to treatment interruption and has not resolved to ≤ grade 1 within 14 days despite infusion interruption
  - grade 3 neurologic event that recurs after dose reduction
  - grade 4 neurologic event
- DLT or other unmanageable toxicity unless a subject has a clear clinical benefit from treatment, the toxicity has resolved to ≤ grade 1 or baseline and after consultation with the sponsor
- in case of re-appearance of the same grade 4 adverse event
- treatment interruption of more than 2 weeks or several interruptions exceeding a total of 14 days of treatment per cycle due to serious adverse events/adverse events
- possible DILI requiring permanent withholding as per Section 7.4.3
- non-manageable GvHD
- subjects who require more than 1 dose reduction
- disease progression as defined by revised IMWG response criteria
- relapse of disease subsequent to response (stringent CR, CR, very good PR, or PR) on protocol treatment.
- occurrence or progression of a medical condition which in the opinion of the investigator should preclude further participation of the subject in the study
- administration of relevant non-permitted concomitant medications
- requirement for alternative therapy
- subject's request

- subject or investigator not compliant with the study protocol
- Women who become pregnant or breastfeed while on treatment (see Section 12.5 for pregnancy and lactation cases reporting requirements)

For grading of events, refer to Section 9.2.3.1.

All reasons for treatment discontinuation should be clearly and comprehensively documented in the eCRF. If a subject has not continued to present for study visits, the investigator should determine the reason and circumstances as completely and accurately as possible.

In any case of premature treatment discontinuation, the investigator should make every effort to perform all examinations scheduled for the end of treatment (EOT).

7.4.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 12.7 for details regarding DILI injury guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product, non-investigational product, or other protocol-required therapies during the study are provided in the IPIM.

7.6 Treatment Compliance

Compliance to treatment and the corresponding assessments should be followed according to the Schedule of Activities (Section 2.2) and the Treatment Procedures (Section 7.1). Refer to the IPIM for additional information.

7.7 Treatment of Overdose

The effects of overdose of this product are not known. The daily AMG 420 dose may be up to 10% lower or higher than specified in the protocol in order to account for possible pump inaccuracies. A dose of up to 10% higher than the intended dose may not require specific intervention.

In case of overdose of > 10% of planned dose, the infusion should be immediately stopped. Consultation with the Amgen medical monitor is required for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage. Consultation with the Amgen medical monitor is also required even if there are no adverse events, in order to discuss further management of the subject. If the overdose

results in clinically apparent or symptomatic adverse events, the subject should be followed carefully until all signs of toxicity are resolved or returned to baseline and the adverse event(s) should be recorded/reported per Section 9.2.3.

Resumption of AMG 420 infusion is possible after consultation with the Amgen medical monitor and should adhere to the guidelines in Section 7.4.2.

A dose of >10% higher than the intended AMG 420 dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 12.4.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were being taken/used from initial diagnosis of multiple myeloma through the start of screening will be collected.

For prior therapies being taken for multiple myeloma, the therapy line, name of therapeutic agent, regimen, type of therapy, start date, and stop date will be collected, as well as best responses.

For radiotherapy the name, site, start date, and stop date will be collected.

For prior autologous or allogeneic HSCT, hematopoietic stem cell mobilization source, conditioning regimen, number of cells infused ($CD34^+$/kg) on day 0, date of neutrophil engraftment (first day that ANC > 0.5 x 10^9/L for 3 consecutive days), date of platelet engraftment (first day that platelets > 20 x 10^9/ L), and complications need to be collected.

7.8.2 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 7.1.7.

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

All concomitant medications, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids will be recorded on the eCRF.

During the LTFU period until EOS, any anti-multiple myeloma treatment is to be recorded.

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

7.8.2.1 Supportive Care

Subjects should receive supportive care according to local guidelines for blood product support, antibiotics, antivirals, analgesics, etc

Please refer to Section 7.4.2.1.2.2 and Section 7.4.2.1.2.5 for management of CRS and infusion related reaction.

Oxygen administration as supportive measure is permitted during study treatment.

To prevent TLS, all subjects should receive at the discretion of the investigator appropriate hydration and supportive measures (eg, rasburicase) according to local standard of care and institutional guidelines. Please refer to Section 7.8.2.7 for management guidelines of TLS.

7.8.2.2 Treatment of Myeloma Bone Disease, Hypercalcemia, Pain, and Renal Failure

Treatment of myeloma bone disease, hypercalcemia, pain, and renal failure should be done according to institutional standards. This may include concurrent treatment with bisphosphonates or denosumab. Radiotherapy for palliative care such as bone pain is only permitted after discussion with Amgen medical monitor.

7.8.2.3 Bone Disease Therapy

Bisphosphonate or other therapy to mitigate myeloma bone disease and associated complications is permitted and should follow investigators' standard of care. Such therapy is ideally administered during weeks between AMG 420 infusions.

7.8.2.4 Intravenous Immunoglobulin Treatment

Intravenous immunoglobulin (IVIG) may be administered to patients per investigators' standard of care, providing this treatment commences following cycle 2 infusion of AMG 420 and is provided during weeks between AMG 420 infusions.

7.8.2.5 Growth Factors

The use of growth factors such as erythropoiesis-stimulating proteins as well as granulocyte colony stimulating factor (G-CSF) will be allowed during therapy per regional and investigator standard of care. However, growth factors are not allowed at inclusion (within 7 days of applicable screening assessment) and should be avoided, if subject`s condition allows, in the first treatment cycle for better assessment of safety parameters.

7.8.2.6 Infections

Prophylactic antibiotics, antifungal, and antivirals are allowed and should be given according to institutional standards. Pneumocystis prophylaxis should also be given according to institutional standards. For subjects who are considered to have an increased risk for herpes infections, prophylaxis is mandatory unless medically contraindicated. Subjects who may experience neutropenia for 7 days or longer are at a high risk for infectious complications. As appropriate, these subjects should be administered prophylactic antibacterial, antifungal, and antiviral medications. These subjects should be monitored for early signs of breakthrough infections after the initiation of antibacterial therapy to prompt additional evaluation and possible therapy modification.

Subjects presenting with evidence of active infection after the start of AMG 420 treatment should be closely monitored while being treated with AMG 420. Subjects with identified, active systemic infections requiring IV antibiotics, antivirals, or antifungals should not be dosed with AMG 420 until infection has resolved, and if being treated with an anti-infectious therapy, the course of such therapy should have been completed.

Patients who develop fever greater than 38.0°C lasting more than 1 hour or fever greater than 38.3°C of any duration during AMG 420 treatment should be promptly evaluated for infection as well as cytokine release syndrome (CRS). Workup should include evaluation for bacterial, fungal, and viral etiologies using radiographic imaging and appropriate microbiological/serologic assays, and empiric therapy should be considered using investigator's institutional standard of care approach. Guidelines for dose interruption and AMG 420 discontinuation as detailed in Tables 7-1 and 7-2 should be followed. Investigators should consider the potential immunosuppressive effects of CRS rescue medications (eg, tocilizumab, corticosteroids) in their empiric management of fever. If patients develop febrile neutropenia (defined as ANC < 1000 10^6/L with a single temperature of > 38.3°C [101°F] or a sustained temperature of ≥ 38°C [100.4°F] for more than one hour), use of standardized guidelines for management and initial treatment of neutropenic fever (eg, Infectious Diseases Society of America Clinical Practice Guidelines, Management of Febrile Neutropaenia: ESMO Clinical Practice Guidelines) is encouraged.

7.8.2.7 Tumor Lysis Syndrome

Tumor Lysis Syndrome is a severe, life-threatening disorder that typically occurs in highly proliferative malignancies. Tumor Lysis Syndrome is frequently observed in patients with hematologic malignancies such as ALL and Burkitt's lymphoma. Tumor Lysis Syndrome is rarely reported in patients with multiple myeloma although patients with a high tumor burden may be at greater risk for TLS (Chang et al, 2011; Cairo et al, 2010). However, given effective new treatments are now available TLS incidence has been reported to be ≤ 5% in patients with multiple myeloma who received different treatments (Howard et al, 2016). Tumor Lysis Syndrome is characterized by a group of metabolic disorders caused by the massive and abrupt release of cellular metabolites into the blood including lactase dehydrogenase (LDH), uric acid, phosphorus, potassium, and calcium after lysis of the malignant cells (Coiffier et al, 2008). The metabolic complications predispose patients with cancer to various clinical complications included renal failure, seizures, cardiac arrhythmias, and even sudden death. To allow for early diagnosis all subjects must be monitored closely for laboratory and clinical evidence of a possible TLS as outlined in Section 12.12 of the protocol.

To prevent TLS, ensure all subjects are well hydrated and provided supportive care measures before administration of AMG 420 as detailed in Section 7.8.2.1. Monitor for evidence of TLS during treatment and manage promptly including interruption of AMG 420 infusion as outlined in Table 7-1. Subjects who experience TLS should be managed according to the local standard of care and institutional guidelines. Supportive therapy, including rasburicase, may be used as clinically indicated at the investigator's discretion.

8. Discontinuation Criteria

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

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 2.2) 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 serious adverse events) and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.3.

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, based on IMWG criteria, in which confirmation of progression requires 2 consecutive laboratory evaluations, except in cases in which progression is based on EM or bone lesions. Laboratory assessments should be separated in time by at least 1 calendar day
- Requirement for alternative therapy
- Pregnancy

8.2 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 12.6 for further details). Refer to the Schedule of Activities (Section 2.2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

Not applicable to this study.

8.2.2 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

8.3 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.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities.

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.

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 21 days. All screening procedures must be performed within 21 days prior to start of investigational product administration, unless otherwise noted. The ICF may be signed earlier than 21 days prior to start of investigational product in case of washout times that have to be observed to meet eligibility criteria.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 6.4) as applicable.

Laboratory assessments used to determine subject eligibility may be repeated once for confirmation during each 21-day screening period before the subject is considered a screen failure. If laboratory assessments are repeated during the screening period, the result of the last sample taken prior to start of treatment with AMG 420 will be taken into account for determination of subject eligibility.

Assessments that were performed as standard of care prior to signature of informed consent, but within 21 days prior to start of treatment with AMG 420 can be used as screening assessments and do not need to be repeated to confirm subject eligibility.

Note: The screening [redacted] sample should be collected on the first day of screening and immediately be sent to the central laboratory. The results should be available prior to start of investigational product treatment.

Re-Screening:

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 2 times at the discretion of the investigator, after consultation with Amgen.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 21-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 21 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

The following assessments do not have to be repeated during re-screening, if they were performed as standard of care or during the initial screening attempt within the time frames specified below:

- Hepatitis serology test does not need to be repeated if they were performed within 6 weeks prior to start of treatment with AMG 420.
- Imaging and BM assessments do not need to be repeated if they were performed within 4 weeks prior to start of treatment with AMG 420.
- Any other assessments do not need to be repeated if they were performed within 21 days prior to start of treatment with AMG 420.
- Plasmacytoma biopsy (if applicable) does not have to be repeated

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 2.2). The date of the first dose of investigational product is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of AMG 420 is to be administered as applicable during each visit that it is required.

Starting with day 4 post infusion, assessments should be performed on the indicated study day, but not at a certain hour of the day. The D6 sample may also be taken on D7 if logistically required (eg, sample cannot be processed at the weekend). Bone marrow assessments post-treatment start may be performed within a window of ± 3 days. Visits during treatment-free interval, if applicable, may occur within a window of ± 1 day.

Furthermore, start of a treatment cycle can be delayed for administrative/logistical reasons for up to 7 days to allow for appropriate scheduling. **Start of treatment cycles later than 7 days from planned next cycle day 1 must only occur** after discussion with and final approval by sponsor. **Delays of treatment cycles beyond 14 days are not permitted.**

The DLRT may implement a ± 1-day window for infusions following the day 1 infusion.

In any case of premature treatment discontinuation prior to day 29 (EOI) the assessments for day 29 do not have to be performed, but the investigator should make every effort to perform all examinations scheduled for the EOT (see Section 2.2).

The expected treatment period is to treat until PD per IMWG (or other protocol-specific reasons as per Section 8.1).

9.1.3 End of Treatment

The EOT visit will occur after last dose of AMG 420. This also applies to subjects who prematurely discontinue investigational product treatment. The EOT visit should occur as soon as possible after the last dose of investigational product was administered. The procedures that will be completed during the EOT visit are designated in the Schedule of Activities (Section 2.2). For subjects who receive second-course treatment, 2 EOT visits will be documented.

9.1.4 Safety Follow-up

The SFU visit should occur 30 (+3) days after the last dose of AMG 420/other protocol-required therapies. Every effort should be made to conduct this visit for all subjects enrolled into the study, including subjects who withdraw from treatment early. The procedures that will be completed during the SFU visit are designated in the Schedule of Activities (Section 2.2).

9.1.5 Long-term Follow-up

Following the SFU visit, there will be a LTFU period for clinical evaluation of disease status and survival. All subjects will be followed every 3 months (± 2 weeks) for survival and anti-multiple myeloma treatment (on-site visits are not required, if needed also interrogation of public databases is acceptable). For subjects who discontinue treatment for reasons other than PD or death, additional on-site visits are required every 6 weeks (± 7 days) for assessments of disease status and documentation of anti-multiple

myeloma treatment until PD. Subjects will be followed for a maximum of 5 years from the first dose of AMG 420, or until subject death, whichever occurs first.

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

The procedures that will be performed during the LTFU are designated in the Schedule of Assessments (Section 2.2) as long as on-site visits apply.

9.1.6 End of Study

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

9.2 Description of General Study Assessments and Procedures

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

9.2.1 General Assessments

9.2.1.1 Informed Consent

A signed ICF must be obtained from each subject prior to any study-mandated procedures. All subjects who are enrolled and receive investigational product treatment should be reconsented with any updated versions of IRB/IEC approved informed consents during study participation as applicable and per institutional guidelines

9.2.1.2 Demographics

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

9.2.1.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started 5 years prior to screening through the time of signing of informed consent. Medical history will include information on the subject's concurrent medical conditions.

Relevant medical history, antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, polyneuropathy, and infection (resolved and ongoing) will be collected. The current toxicity grade will be collected for each condition that has not resolved.

Multiple myeloma history must date back to the initial diagnosis and any response duration must be recorded.

All findings will be recorded on the Medical History eCRF.

9.2.1.4 Physical Examination

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

A complete physical examination as per standard of care will be performed by the investigator or designee at screening and at the time points specified in the Schedule of Activities (Section 2.2). The physical examination will include general appearance, including examination of the skin, spleen, and 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.

9.2.1.5 Physical Measurements

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

9.2.1.6 Performance Status

The performance status will be assessed at the time points indicated in the Schedule of Activities (Section 2.2) using the ECOG performance status scale (see Section 12.14).

9.2.2 Efficacy Assessments

9.2.2.1 Blood and Bone Marrow

Blood and BM samples are to be collected for biomarker assessments and development, and safety and response assessments at time points specified in the Schedule of Activities (Section 2.2).

Samples will be investigated by local and central laboratories as specified in Section 12.2 .

Refer to the laboratory manual for detailed collection and handling procedures.

9.2.2.2 SPEP, UPEP, and Tumor Assessment

Serum protein electrophoresis (SPEP) and 24-hour UPEP are required for all subjects as indicated in the Schedule of Activities (Section 2.2). Immunofixation is required at screening and should be repeated as shown in Schedule of Activities (Section 2.2). Urine immunofixation (UIFE) is not required to be repeated if negative at baseline. Assessments will be performed centrally.

Tumor assessment will be done by analysis of percent myeloma involvement, fluorescence in situ hybridization (FISH) as well as karyotyping in BM. BM FISH/karyotyping will be performed locally. Analysis of percent myeloma involvement will be assessed centrally. Data for BM karyotyping and FISH may be obtained from a BM sample obtained as part of standard of care within 120 days prior to treatment start with investigational product.

Further BM samples will be required as described in the Schedule of Activities (Section 2.2).

9.2.2.3 Serum Free Light Chain

Serum free light chain assay and ratio will be performed at each time point as specified in the Schedule of Activities (Section 2.2). In case of free light chain (FLC) multiple myeloma (M-protein negative cases), FLC will be analyzed in serum and urine at the same time points as for SPEP/UPEP described above. Levels of involved/uninvolved FLC, ratio of monoclonal λFLC/κFLC, and ratio of monoclonal κFLC/λFLC will be determined.

9.2.2.4 Quantitative Immunoglobulin

Quantitative immunoglobulin (Ig) will be performed at screening and at time points indicated in the Schedule of Activities (Section 2.2). In addition, quantitative immunoglobulin will be repeated if clinically indicated, ie, frequent infection despite multiple myeloma disease control or deemed clinically indicated by the investigator.

9.2.2.5 Beta-2 Microglobulin

Beta-2 microglobulin in serum will be assessed at screening as part of risk stratification and during the study as indicated in the Schedule of Activities (Section 2.2).

9.2.2.6 Skeletal Survey/Plasmacytoma Assessments

Skeletal survey and plasmacytoma assessments (if applicable) will be performed at time points specified in the Schedule of Activities (Section 2.2). Results from prior

assessment for multiple myeloma if one of these techniques were used are acceptable for screening if performed within 30 days before cycle 1 day 1. The same technique must be employed for each measurement. Imaging studies will be read locally. Bi-dimensional lesion measurements (SPD; sum of the products of the maximal perpendicular diameters of measured lesions) for skeletal lesions (lytic or plasmacytoma) and for extrameduallary lesions must be performed and recorded in the designated eCRF.

All subjects are required to have screening imaging to evaluate for EM relapse using whole-body MRI or PET/CT.

A skeletal survey is required if no other imaging appropriate for assessment of bone lesions is performed.

For subjects who have whole-body MRI for plasmacytoma assessment, a separate skeletal assessment to detect lytic bone lesions is required (skeletal x-ray, low dose whole body computed tomography (CT), or FDG PET/CT). For subjects, who have positron emission tomography (PET)/computed tomography (CT) imaging for plasmacytoma assessment, a separate skeletal survey to detect lytic bone lesions is not required.

Extramedullary plasmacytoma assessments should be repeated every 12 weeks (± 2 weeks) during treatment to confirm a PR or better only if measurable plasmacytoma are present at baseline, or if clinically indicated. Skeletal lesion assessments should be repeated only as clinically indicated. The same technique (may include CT scan, MRI, PET, PET-CT, or other standard-of-care method) must be employed for each measurement. SPD must be performed and recorded in the designated eCRF.

Skeletal survey is not required for confirmation of PR or better.

9.2.2.7 Minimal Residual Disease

Minimal residual disease in BM is a mandatory biomarker measurement in this study. Minimal residual disease will be measured centrally by a [redacted]. Bone marrow aspirates will be collected at specific time points for subjects suspected to be complete responders, according to the Schedule of Activities (Section 2.2). The BM aspirates will be processed and stored according to a protocol that is provided to the central lab.

[redacted]

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Section 2.2).

9.2.3.1 Adverse Events

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

9.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE and is described in Section 12.4, with the following exceptions: CRS will be graded according to the criteria referenced in the publication by Lee et al (2014) described in Section 7.4.2.1.2.5 and TLS will be graded based on Cairo-Bishop criteria (Coiffier et al, 2008) described in Section 12.12.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product or other protocol-required therapies, whichever occurs first through the safety follow-up visit (30 [+3] days after last dosing interval of investigational product) are reported using the Event eCRF.

9.2.3.1.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through **safety follow-up visit or 30 days after last day of dosing interval of investigational product(s)/protocol-required therapies**, **whichever occurs later** are reported using the Event**s** eCRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours following the investigator's knowledge of the event, as indicated in Section 12.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

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

9.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period

If the investigator becomes aware of serious adverse events **suspected to be related to IP after** the protocol-required reporting period **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. In addition, the investigator will need to collect/report fatal serious adverse events (regardless of causality) to Amgen within 24 hours following the investigator's awareness of the events on the Events CRF.**

After End of Study, there is no requirement to actively monitor study subjects for serious adverse events. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event.

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

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

9.2.3.1.2 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.

9.2.3.1.3 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 8.3). Further information on follow-up procedures is given in Section 12.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as

discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event eCRF.

9.2.3.1.4 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.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until 6 weeks after the last dose of AMG 420 or in a male subject's female partner through 14 weeks after the last dose of AMG 420.

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

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

Further details regarding pregnancy and lactation are provided in Section 12.5.

9.2.3.1.6 Safety Monitoring Plan

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

9.2.3.2 Vital Signs

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

9.2.3.3 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. ECGs should be performed in a standardized method, in triplicate, and run consecutively (ie, approximately 60 seconds apart), prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

- ≥ 3 baseline ECGs collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (ie, approximately 60 seconds apart) [ie, total ≥ 9 ECGs]
- Single ECGs at time points after dosing

The Baseline ECG QTc (defined as the average of the individual baseline ECGs), should not be > 470 msec (applying Fridericia correction). Baseline is defined as predose assessments from cycle 1 day 1. The investigator or designated site physician will review all ECGs. ECGs will be transferred electronically to an ECG central reader for analysis per Amgen instructions. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Standard ECG machines should be used for all study-related ECG requirements.

9.2.3.4 Vital Status

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

9.2.3.5 Other Safety

9.2.3.5.1 Pulse Oximetry

Oxygen saturation will be measured using a standard pulse oximeter. The subject must be in a rested and calm state for at least 5 minutes before pulse oximetry assessments are completed.

9.2.3.5.2 Peripheral Neuropathy

The peripheral neuropathy assessment should be done at screening and time points specified in the Schedule of Activities (Section 2.2). All assessments must be reported on the corresponding eCRF page (see Section 12.16) for peripheral neuropathy assessment tool. Assessments will include historical information on neuropathy symptoms, including relationship to prior anti-MM therapies, severity and duration of symptoms.

9.2.4 Clinical Laboratory Assessments

Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 2.2) for the timing and frequency.

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

All protocol-required laboratory assessments, as defined in Section 12.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 2.2).

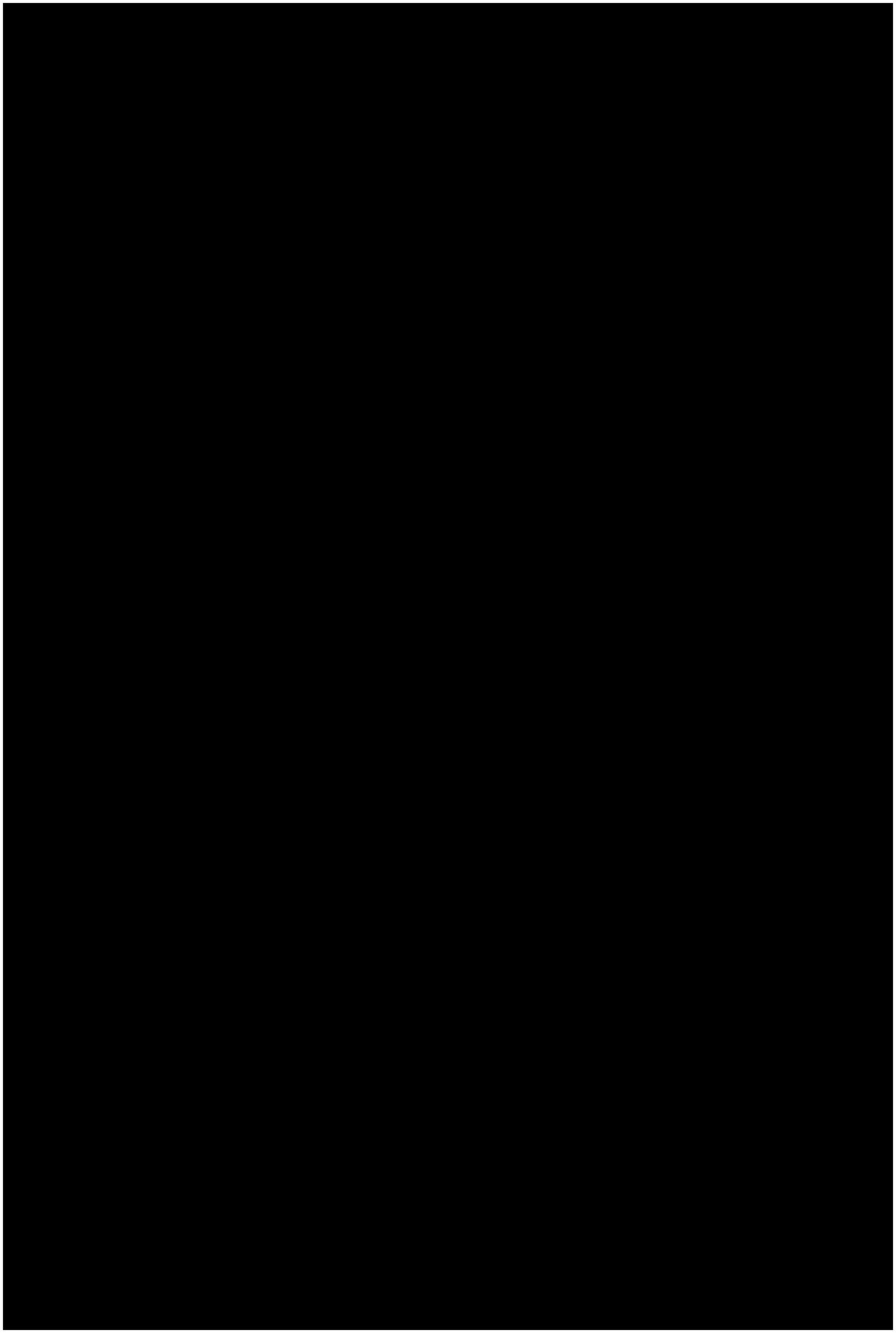
9.2.4.1 Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential. In the case of a positive urine result. A serum pregnancy test should be performed for confirmation.

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 Worksheet, see Figure 12-2). Refer to Section 12.5 for contraceptive requirements.

Additional pregnancy testing (serum or urine) during treatment with protocol-required therapies will be performed as indicated in Section 2.2 and at the safety follow-up.

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



[redacted]

9.2.5 Pharmacokinetic Assessments

All subjects enrolled will have pharmacokinetic samples assessed.

Whole blood samples of approximately 2 mL will be collected for measurement of serum concentrations of AMG 420 as specified in the Schedule of Activities (Section 2.2). 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.

9.2.6 Pharmacodynamic Assessments

Venous blood samples of approximately 20 mL per visit will be collected for measurement of AMG 420 response.

[redacted]

[redacted]

[redacted]

9.2.9 Biomarker Development

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

In oncology, there is a particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or protocol-required therapies.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 420 to investigate and further understand multiple myeloma.

Exploratory assays – [redacted]

[redacted]

[redacted]

10. Statistical Considerations

10.1 Sample Size Determination

Approximately 20 subjects will be enrolled (approximately 10 treated at the 400 μg/day dose level and approximately 10 treated at the 600 μg/day dose level).

The sample size is based on practical considerations and it is consistent with the number of subjects enrolled in a dose expansion cohort of a conventional, oncology phase 1 study. With 10 subjects treated at a dose level/schedule, there is a 65% to 89% probability of observing an adverse event if the true event rate is 10% to 20%.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 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 1 dose of AMG 420. An overall assessment of safety with monotherapy treatment will be conducted on the Monotherapy Safety Analysis Set defined as all subjects that are enrolled in the study and receive at least 1 dose of AMG 420. The analysis of DLT will be restricted to DLT-evaluable subjects (see Section 7.4.1). The analysis of DOR will be restricted to subjects with a partial response or better. DLT evaluation analysis set includes subjects complete the DLT evaluable period or experienced a DLT any time during the DLT evaluable period. The PK Analysis Set will contain all subjects who have received at least 1 dose of the investigational product and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

10.2.2 Covariates

There are no planned covariates in this study.

10.2.3 Subgroups

Subgroup analyses will be performed for the primary and secondary efficacy endpoints. The baseline variables for the subgroup analyses may include:

- baseline demographics and characteristics:
  - age (< 65, 65-74, ≥ 75 years)
  - sex (female, male)
  - race (White, Asian, other)
- baseline disease characteristics:

  - revised International Staging System (ISS) stage (Stage I, Stages II or III)
  - BM percent of plasma cells (< 50%, ≥ 50%)
  - [redacted]
  - [redacted]
  - extramedullary disease (yes, no). Until safety evaluation is complete for 3 subjects with EM disease, imaging evaluation at screening will be used to document EM disease status as described in Section 9.2.2.6. After DLRT confirms safety in setting of EM disease, EM disease status will utilize investigator assignment.
- number of prior lines of therapy (only 3, > 3)
- prior allogeneic HSCT (yes, no)
- refractory to
  - IMiD (yes, no)
  - PI (yes, no)
  - IMiD + PI (yes, no)
  - daratumumab or other CD 38-targeting antibody (yes, no)

In addition, safety in the subgroup of subjects with EM disease will be reviewed.

Subgroup analysis will not be performed if the sample size within a subgroup is too small. Details will be documented in statistical analysis plan

10.2.4 Handling of Missing and Incomplete Data

The descriptive statistics will identify the extent of missing data. Missing or incomplete dates that are critical to efficacy and safety analysis, for example, death date and adverse event start dates, will be imputed. Detailed imputation rules will be documented in statistical analysis plan.

10.3 Adaptive Design

The rules for halting enrollment, or dose de-escalation, are based on an mTPI design. 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. Enrollment recommendations 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 TPI: DLT rate > 33%

For the current dose level and after adjusting for the width of each TPI interval, if the DLT rate is most likely in the under-dosing TPI or most likely in the target TPI then the recommendation is to continue enrollment at the current level. If the DLT rate is most likely in the over-dosing TPI then the recommendation is to halt enrollment.

10.4 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 5.3.1.

10.4.1 Planned Analyses

10.4.1.1 Interim Analysis and Early Stopping Guidelines

10.4.1.1.1 Interim Analyses

10.4.1.1.1.1 Safety data will be reviewed by the DLRT on an ongoing basis with the possibility of early termination of enrollment, as described in Section 5.1. Dose Level Review Team

A DLRT will be responsible for monitoring safety and making recommendations regarding termination of enrollment and dose level/schedule changes.

See Section 12.3 for further details of DLRT responsibilities.

10.4.1.2 Primary Analysis

The primary analysis will occur when the target enrollment is complete and each subject has had the chance to be treated for at least 6 months.

10.4.1.3 Final Analysis

A final analysis is planned after all subjects have ended the study.

10.4.2 Methods of Analyses

10.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamic and biomarker data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Time to event endpoints will be summarized with Kaplain-Meier (KM) proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and censoring

reasons. Duration of follow-up for time to event endpoints will be estimated using the reverse Kaplan Meier method (Schemper and Smith, 1996). Point estimates for efficacy endpoints will be accompanied by 2-sided 95% confidence intervals including KM quartiles (Klein and Moeschberger, 1997), KM proportions (Kalbfleisch and Prentice, 1980), and binomial proportions (Clopper and Pearson, 1934). Graphical summaries of the data may also be presented.

10.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable for phase 1b.
Secondary	Tabular summaries of efficacy endpoints will be reported separately by dose level and part. For subjects included in the Safety Analysis Set, the proportion of subjects with BOR of PR or better per IMWG and MRD negativity at the time of CR will be calculated and tabulated. DOR and time to response analyses will be done for subjects who are in Safety Analysis Set and have a best overall response of PR or better. The percentage of subjects with extended TFI of 4 weeks at approximately 6 months and 4 weeks or 8 weeks at approximately 12 months, out of all treated subjects and out of those who are eligible based on response status (only patients with MRD-negative CR at these landmark times are eligible for the extended TFI calculation). If appropriate, KM proportions at select time points, KM quartiles (when estimable) and KM curves will be provided for DOR, PFS, and OS. Descriptive statistics including median and range will be provided for time to response. Listings will be produced for all subjects indicating the MRD negativity, OS, PFS, time to response, and DOR.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.4.2.3 Safety Analyses

10.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	The primary endpoints are safety endpoints. Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the Safety Analysis Set, which includes subjects that are enrolled and received at least 1 dose of AMG 420. Descriptive statistics for safety endpoints will be tabulated overall and by dose level and part. **Adverse Events** Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. The number and percentage of subjects reporting adverse events will be evaluated overall and by AMG 420 dose level and part will also be tabulated by relationship to AMG 420. Tables of adverse events, fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other

Endpoint	Statistical Analysis Methods
	protocol-required therapies, and significant treatment-emergent adverse events will also be provided. **Dose Limiting Toxicities** The analysis of the probability of DLTs will include data from DLT-evaluable subjects (see Section 7.4.1 for definition of DLT-evaluable). The primary analysis will only include DLTs that occur within the first cycle. If DLTs occur outside the first cycle, a sensitivity analysis will be performed where DLTs occurring outside of the specified time interval are included. The number and percentage of subjects reporting DLTs will be evaluated overall and by AMG 420 dose level and part. **Clinical Laboratory Tests** Clinical chemistry, hematology, and urinalysis data will be listed and reviewed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory data, the analyses of safety laboratory endpoints will include summary statistics over time and/or changes from baseline over time. Maximum shifts in grades of selected safety laboratory values between baseline and the worst on-study value may be tabulated. **Vital Signs** Vital signs data will be listed and reviewed for each subject. Depending on the size and scope of changes, the analyses of vital signs may include summary statistics over time and/or changes from baseline over time. **Electrocardiograms** Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QTcF will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized. All on-study ECG data will be listed, and select parameters of interest may be plotted.

10.4.2.3.2 Adverse Events

Statistical analysis on adverse events is described in Section 10.4.2.3.1.

10.4.2.3.3 Laboratory Test Results

Statistical analysis on laboratory test results is described in Section 10.4.2.3.1.

10.4.2.3.4 Vital Signs

Statistical analysis on vital signs is described in Section 10.4.2.3.1.

10.4.2.3.5 Physical Measurements

The analyses of physical measurements will include summary statistics at baseline.

10.4.2.3.6 Electrocardiogram

Statistical analysis on electrocardiogram data is described in Section 10.4.2.3.1.

[redacted]

10.4.2.3.8 Exposure to Investigational Product

The average dose per administration (μg), cumulative dose (μg), number of cycles, duration of usage, number and percentage of subjects with dose modifications, reasons for modification will be summarized using descriptive statistics. Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given.

10.4.2.3.9 Exposure to Concomitant Medication

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

10.4.2.4 Other Analyses

10.4.2.4.1 PK Analyses

The PK parameters of AMG 420 including, but not limited to, average C_{ss}, clearance, and half-life ($t_{1/2}$) for serum AMG 420 will be estimated using non-compartmental methods and summarized by dose level using means, geometric means, standard deviations, coefficients of variation, medians, minimums, and maximums. Individual concentration-time profiles will be summarized by dose level. Plasma AMG 420 concentrations at each time point along with PK parameter values may be listed for each subject. Summary statistics will be computed for each sampling time and parameter as appropriate. The relationship between AMG 420 exposure and efficacy/safety may be conducted.

11. References

AMG 420 Investigator's Brochure. Thousand Oaks, CA: Amgen Inc.

Avery DT, Kalled SL, Ellyard JI, et al, BAFF selectively enhances the survival of plasmablasts generated from human memory B cells. *J Clin Invest*. 2003;112:286-297.

Avet-Loiseau H, Attal M, Moreau P, et al, Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood.* 2007;109(8):3489–3495.

Benjamin JE, Stein AS. The role of blinatumomab in patients with relapsed/refractory acute lymphoblastic leukemia. *Ther Adv Hematol.* 2016;7(3):142-156.

Berdeja JG, Lin Y, Raje N, et al, Clinical remissions and limited toxicity in a first-in-human multicenter study of bb2121, a novel anti-BCMA CAR T cell therapy for relapsed/refractory multiple myeloma. *Eur J Cancer.* 2016;68(Supplement 1):S5.

Cairo MS, Coiffer B, Reiter A, et al, Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant disease: an expert TLS panel consensus. *Br J Haematol*. 2010;149(4):578-586.

Carpenter RO, Evbuomwan MO, Pittaluga S, et al, B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. *Clin Cancer Res*. 2013;19(8):2048-2060.

Chanan-Khan AA, Giralt S. Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. *J Clin Oncol*. 2010;28:2612-2624.

Chang H, Lee SY, Tang TC. Tumor lysis syndrome in patients with light chain multiple myeloma: report of two cases. *Chang Gung Med J*. 2011;34(6 Suppl):70-75.

Chiu A, Xu W, He B, et al, Hodgkin lymphoma cells express TACI and BCMA receptors and generated survival and proliferation signals in response to BAFF and APRIL. *Blood.* 2007;109(2):729-739.

Cohen AD, Garfall AL, Stadtmauer EA, et al, B-Cell Maturation Antigen (BCMA)-Specific Chimeric Antigen Receptor T Cells (CART-BCMA) for Multiple Myeloma (MM): Initial Safety and Efficacy from a Phase I Study. *Blood*. 2016;128:1147.

Cook G, Zweegman S, Mateos MV, Suzan F, Moreau P. A question of class: Treatment options for patients with relapsed and/or refractory multiple myeloma. *Crit Rev Oncol Hematol*. 2018;121:74-89.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika.* 1934;26(4):404-413.

Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol.* 2008;26(16):2767-2778.

Dimopoulos MA, Oriol A, Nahi H, et al, Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med.* 2016;375(14):1319-1331.

Dimopoulos MA, Richardson PG, Moreau P, Anderson KC. Current treatment landscape for relapsed and/or refractory multiple myeloma. *Nat Rev Clin Oncol.* 2015;12:42–54.

Drug Facts and Comparison 2006. 60th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.

Durie BG. *Multiple Myeloma Cancer of the Bone Marrow. Concise Review of the Disease and Treatment Options*. International Myeloma Foundation, 2011/2012.

Frankel SR, Baeuerle PA. Targeting T cells to tumor cells using bispecific antibodies. *Curr Opin Chem Biol.* 2013;17(3):385-392.

Ghermezi M, Li M, Vardanyan S, et al, Serum B-cell maturation antigen: a novel biomarker to predict outcomes for multiple myeloma patients. *Haematologica.* 2017;102(4):785-795.

Gross JA, Johnston J, Mudri S, et al, TACI and BCMA are receptors for a TNF homologue implicated in B-Cell autoimmune disease. *Nature*. 2000;404(6781):995-999.

Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York City, NY: McGraw Hill Professional; 1996.

Howard SC, Trifilio S, Gregory TK, Baxter N, McBride A. Tumor lysis syndrome in the era of novel and targeted agents in patients with hematologic malignancies: a systematic review. *Ann Hematol*. 2016;95(4):563-573.

Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. *Clin Trials.* 2010;7(6):653-663.

Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data, Hoboken, New Jersey: John Wiley & Sons; 1980.

Kantarjian H, Stein A, Goekbuget N, et al, Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med.* 2017;376(9):836-847.

Klein JP, Moeschberger ML. Survival Analysis: Techniques for Censored and Truncated Data, New York: Springer-Verlag; 1997.

Kumar S, Paiva B, Anderson KC, et al, International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* 2016;17(8):e328-346.

Kumar SK, Lee JH, Lahuerta JJ, et al, Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia*. 2012;26(1):149-157.

Novak AJ, Darce JR, Arendt BK, et al, Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a mechanism for growth and survival. *Blood*. 2004 Jan 15;103(2):689-94.

Richardson PG, Sonneveld P, Schuster MW, et al, Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood*. 2007;110(10):3557–60.

Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials.* 1996;17(4):343–46.

Smith EM, Cohen JA, Pett MA, Beck SL. The Reliability and Validity of a Modified Total Neuropathy Score-Reduced and Neuropathic Pain Severity Items When Used to Measure Chemotherapy-induced Peripheral Neuropathy in Patients Receiving Taxanes and Platinums. *Cancer Nurs.* 2010;33(3):173-183.

Lee DW, Gardner R, Porter DL, et al, Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195. Erratum in: *Blood.* 2015;126(8):1048. Dosage error in article text.

Lonial S, Dimopoulos M, Palumbo A, et al, Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *N Engl J Med.* 2015;373(7):621-631.

Madry C, Labbi Y, Callebaut I, et al, The characterization of murine BCMA gene defines it as a new member of the tumor necrosis factor receptor superfamily. *Int Immunol*. 1998;10(11):1693-1702.

Moreaux J, Legouffe E, Jourdan E, et al, BAFF and APRIL protect myeloma cells from apoptosis induced by interleukin 6 deprivation and dexamethasone. *Blood*. 2004;103(8):3148-3157.

Nagorsen D, Kufer P, Baeurle PA, Bargou R. Blinatumomab: a historical perspective. *Pharmacol Ther.* 2012;136(3):334-342.

O'Connor BP, Raman VS, Erickson LD, et al, BCMA is essential for the survival of long-lived bone marrow plasma cells. *J Exp Med.* 2004;199(1):91-98.

Oken MM, Creech RH, Tormey DC, et al, Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.

Palumbo A, Chanan-Khan A, Weisel K, et al, Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *N Engl J Med.* 2016;375(8):754-766.

Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med.* 2011;364(11):1046-1060.

Panowski SH, Kuo T, Chen A, et al, Preclinical Evaluation of a Potent Anti-Bcma CD3 Bispecific Molecule for the Treatment of Multiple Myeloma. *Blood*. 2016;128:383.

Papadas A, Asimakopoulos F. Mechanisms of Resistance in Multiple Myeloma. *Handb Exp Pharmacol.* 2017.

Physician's Desk Reference 2002: PDR Library/Hospital Edition. 56th ed. Montvale, NJ: Medical Economics Company; 2002.

Rajkumar SV, Dimopoulos MA, Palumbo A, et al, International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15(12):e538-548.

Rajkumar SV, Harousseau JL, Durie B, et al, Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood.* 2011;117(18):4691-4695.

Sanchez E, Li M, Kitto A, et al, Serum B-cell maturation antigen is elevated in multiple myeloma and correlates with disease status and survival. *Br J Haematol.* 2012;158(6):727-738.

SEER Stat fact sheets: myeloma. U.S. Department of Health & Human Services, National Institutes of Health, National Cancer Institute, Surveillance Epidemiology and End Results (SEER) 2014.

Siegel R, Miller KD, Jemal A. Cancer Statistic 2015. *CA Cancer J Clin.* 2015;65:5–29.

Smith D, Yong K. Multiple myeloma. *BMJ.* 2013;346:f3863.

Tai YT, Li XF, Breitkreutz I, et al, Role of B-cell-activating factor in adhesion and growth of human multiple myeloma cells in the bone marrow microenvironment. *Cancer Res.* 2006;66(13):6675-6682.

Thompson JS, Bixler SA, Qian F, et al, BAFF-R, a newly identified TNF receptor that specifically interacts with BAFF. *Science.* 2001;293(5537):2108-2111.

Topp MS, Goekbuget N, Stein AS, et al, Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol.* 2015;16(1):57-66.

Topp MS, Goekbuget N, Zugmaier G, et al, Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol.* 2014;32(36):4134-4140.

United States Food and Drug Administration. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. https://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

Von Stackelberg A, Locatelli F, Zugmaier G, et al, Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. *J Clin Oncol*. 2016;34(36):4381-4389.

Yu G, Boone T, Delaney J, et al, APRIL and TALL-1 and receptors BCMA and TACI: system for regulating humoral immunity. *Nat. Immunol.* 2000;1(3):252-256.

Yuraszeck T, Kasichayanula S, Benjamin JE. Translation and Clinical Development of Bispecific T cell Engaging Antibodies for Cancer Treatment. *Clin Pharmacol Ther.* 2017;101(5):634-645.

Zhao C, Inoue J, Imoto I, et al, Pou2AF1, an amplification target at 11q23, promotes growth of multiple myeloma cells by directly regulating expression of B-cell maturation factor, TNFRSF17. *Oncogene.* 2008;27:63-75.

12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ADL	activities of daily living
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APRIL	a proliferation-inducing ligand
AST	aspartate aminotransferase
AUC_{last}	area under the concentration-time curve from time 0 to the last measurable concentration
BAFF	B-cell activating factor
BAFF-R	B-cell activating factor receptor
BCMA	B-cell maturation antigen
BI	Boehringer Ingelheim
BiTE®	bispecific T-cell engager
BM	bone marrow
BOR	best overall response
CAR	chimeric antigen receptor
CBC	complete blood count
cIV	continuous intravenous
C_{max}	maximum concentration
CR	complete response
CRP	C-reactive protein
CRS	cytokine release syndrome
C_{ss}	steady-state concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DILI	drug-induced liver injury
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose limiting toxicity
DOR	duration of response

Abbreviation or Term	Definition/Explanation
DRT	data review team
EC_{50}	half-maximal target cell lysis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EM	extramedullary
EMA	European Medicines Agency
EOI	end of infusion
EOS	end of study
EOT	end of treatment
FCBP	females of childbearing potential
FDA	Food and Drug Administration
FDG PET	fluorodeoxyglucose positron emission tomography
FIH	first-in-human
FISH	fluorescent in situ hybridization
FLC	free light chain
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
GHS	global health status
GLP	good laboratory practice
GvHD	graft versus host disease
H_2 blocker	histamine 2 blocker
HbA1c	glycosylated hemoglobin
HepBsAg	hepatitis B surface antigen
HepCAb	hepatitis C virus antibody
HHCS	home health care service
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN-γ	interferon-γ
Ig	immunoglobulin

Abbreviation or Term	Definition/Explanation
IL	interleukin
IMiD	immunomodulator
IMWG	International Myeloma Working Group
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
ISS	International Staging System
IUD	intrauterine device
IV	intravenous(ly)
IVSS	intravenous solution stabilizer
KM	Kaplan-Meier
LDH	lactase dehydrogenase
LTFU	long-term follow-up
MDE	myeloma defining event
MDSCs	myeloid derived suppressor cells
MGUS	monoclonal gammopathy of undetermined clinical significance
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
[redacted]	[redacted]
NIMP	non-investigational medicinal products
NK cells	natural killer cells
NOD/SCID	non-obese diabetic/severe combined immunodeficiency
ORR	overall response rate
OS	overall survival
PB	peripheral blood
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PF	physical functioning

Abbreviation or Term	Definition/Explanation
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
POEMS	POEMS syndrome: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PR	partial response
PRO	Patient-Reported Outcomes
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PSA	prostate specific antigen
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG or partial response
QoL	Quality of Life
QRS interval	QRS interval is the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QTcF	Fridericia's Correction Formula
QTc interval	QT interval corrected for heart rate using accepted methodology
RRMM	Relapsed and/or refractory multiple myeloma
SARS-COV-2	**severe acute respiratory syndrome coronavirus 2**
SC	subcutaneous(ly)
sFLC	serum free light chain
SFU	safety follow-up
SPD	bi-dimensional lesion measurements (sum of the products of the maximal perpendicular diameters of measured lesions)
SPEP	serum protein electrophoresis
$t_{1/2}$	half-life
TACI	transmembrane activator and calcium modulator
TB	tuberculosis
TBL	total bilirubin
TFI	treatment-free interval
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
TPI	toxicity probability interval
T_{reg} cells	regulatory T cells
UIFE	urine immunofixation

Abbreviation or Term	Definition/Explanation
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VAS	visual analog scale
VGPR	very good partial response
WFI	Water for Injection

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the central laboratory and/or by the local laboratory. **Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).**

The date and exact time of sample collection will be recorded in the source documents at the site (do not use the time that the samples were frozen or any other time point).

If blood samples are collected on the same day on which the infusion bag is being changed, the blood samples must be collected before the infusion bag is changed.

Blood draws should not be done via central venous access. Exception: if a permanent central line with more than one lumen is used, blood draws can be done via the lumen that is not used for AMG 420 drug administration.

The test results are to be recorded on the electronic case report forms (eCRFs). Missed test(s) that are not done must be reported as such on the eCRFs.

Refer to the laboratory manual and/or Amgen-provided training materials for detailed collection, processing, and shipping instructions.

Additional procedures (eg, collection of an unscheduled blood sample to measure cytokine levels) deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the investigator's discretion.

Where required by local laws or regulations, additional assessments are defined in a country-specific protocol supplement at the end of the Appendix Section of protocol.

Table 12-1. Analyte Listing

Local Laboratory					Central Laboratory
Chemistry	Hematology	Coagulation	Urinalysis	Other	
Sodium Potassium Chloride Bicarbonate (HCO_3) or Total CO_2 Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine[a] Uric acid Total bilirubin Direct bilirubin ALP ALT (SGPT) AST (SGOT) Amylase Lipase LDH Ferritin CRP	ANC Hemoglobin Hematocrit MCH MCHC MCV Platelets RBC WBC Differential • Total neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes • Plasma cells	PT or INR PTT Fibrinogen D-Dimer	Specific gravity pH Blood Protein Ketones Glucose Bilirubin Leucocytes esterase (WBC) Microscopic exam (only needed for positive dipstick and should include the following): Epithelial, Bacteria, Casts, Crystal, RBC, WBC	Serology (Hep B, Hep C) Latent tuberculosis test Urine or serum pregnancy test[b] Immunoglobulins (IgA, IgM, IgG) BM FISH/karyotyping	[redacted] PK sampling [redacted] MRD [redacted] % MM involvement sCR SPEP UPEP sFLC sβ-2 microglobulin

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; [redacted]; BSA = body surface area; BUN = blood urea nitrogen; CRP = C-reactive protein; [redacted]; FISH = fluorescent in-situ hybridization; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactase dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MM = multiple myeloma; MRD = minimal residual disease; PB = peripheral blood; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; [redacted]; sFLC = serum free light chain; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; WBC = white blood cells sCR= stringent Complete Response

[a] Creatinine clearance will be calculated using the Cockcroft-Gault equation: (140 - age [years] x weight [kg] x 0.85 if female) / (72 x creatinine mg/dL), adjusted for BSA by 1.73 m^2/BSA.

[b] A pregnancy test will be performed locally at each site on all women unless they are surgically sterile or ≥ 2 years postmenopausal.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

12.3 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 escalation/change, changes in dosing schedule, and minimum hospitalization. In phase 1b, the DLRT will convene and review all available safety, laboratory, and PK data at the following scheduled time points:

- After at least 10 subjects in phase 1b cohort 1 (400 μg/day dose level) have had the opportunity to complete the 4-week infusion period of the first treatment cycle: On the basis of this review, the DLRT will make a recommendation regarding the initiation of phase 1b cohort 2 (600 μg/day dose level).
- After at least 3 subjects with extramedullary (EM) relapsed disease in phase 1b cohort 1 (400 μg/day dose level) have had the opportunity to complete the 4-week infusion period of the first treatment cycle: On the basis of this review, the DLRT will make a recommendation regarding the appropriateness of continued enrollment of subjects with EM relapsed disease in phase 1b cohort 2 (600 μg/day dose level). Please note that enrollment of subjects with EM relapsed disease in phase 1b cohort 2 will not be allowed until this safety review of the first 3 subjects with EM disease is completed by the DLRT.
- After the first 3 subjects have been dosed with AMG 420 at 600 μg/day for the full 4-week infusion cycle in phase 1b cohort 2.

The DLRT may also convene ad hoc meetings any time to review safety data if deemed necessary. The DLRT will be composed of the investigators or designees, and the following Amgen representatives: early development lead or designee, global safety officer or designee, clinical study manager, biostatistician, pharmacokinetics (PK) scientist (optional), and other functional area representatives as appropriate. The following members are responsible for DLRT recommendations: investigators, Amgen early development lead or designee, and global safety officer or designee.

A quorum must be in attendance for the dose level review meeting (DLRM). The quorum is defined as ≥ 50% of the participating investigators or their qualified designee (ie, sub-investigator or research nurse or study coordinator), as well as > 50% of Amgen representatives listed above. Investigators that are not able to participate in the meeting (eg, due to time difference) may also provide their recommendations in writing after review of the data discussed at the meeting. The early development lead or designee and the global safety officer or designee must attend for the quorum to be reached. The DLRM will be rescheduled if a quorum is not reached.

Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and 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 **that Amgen distributes to the site**. 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 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 8.

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

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

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

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 21 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 eCRF 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 eCRF 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 eCRF.

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 Interactive Response Technology (IRT) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

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

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

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the [IRB/IEC] and Amgen
- Investigational product-related correspondence including [Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

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

Study and Site Closure

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

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

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

Compensation

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

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

Definition of Adverse Event

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

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

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/serious adverse event information in the Event eCRF. • 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;** o **Assessment of seriousness** o Severity (or toxicity defined below); o Assessment of relatedness to investigational product**,** other protocol-required therapies, study-mandated 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.

Adverse Event and Serious Adverse Event Recording
• 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 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. with the exception of cytokine release syndrome (CRS), which must be graded using the criteria referenced in the publication by Lee et al, 2014 (see Section 7.4.2.1.2.5) and tumor lysis syndrome (TLS), which must be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al, 2008 (see Section 12.12).
Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product, protocol-required therapies or study-mandated procedure and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure 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 9.2.3.1.1, 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 via the Safety Report Form.
- If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Contingency Report Form (see Figure 12-1) within 24 hours of the investigator's knowledge of the event.
- The site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form.

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Report Form

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

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

General Instructions

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

Types of Events to be reported on this form

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

1. **Site Information**

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

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

2. **Subject Information**

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

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

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

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

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –

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

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

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

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

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

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

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

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

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

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

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

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

4. **Hospitalization**

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

FORM-056006 *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.*

AMGEN
Study # 20160370
AMG 420

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 420 No / Yes	[redacted] No / Yes	[redacted] No / Yes	[redacted] No / Yes	Outcome of Event 1-Resolved 2-Not resolved 3-Fatal 4-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 420	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20160370 AMG 420	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Test											
Unit											
Date (Day Month Year)											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20160370 AMG 420	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

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

Study-specific contraception requirements for male and female of childbearing potential are outlined in Section 6.2.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 6 weeks (or for 14 weeks a male subject's female partner) after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

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

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

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

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

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

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

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

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

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 14 weeks 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 weeks after the last dose of AMG 420.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet 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 Worksheet 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 weeks after the last dose of AMG 420 of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 12.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.

- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 14 weeks after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet.
- The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet 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 weeks after the last dose of AMG 420.
- Information will be recorded on the Lactation Notification Worksheet (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 22**4**.
- 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 weeks after the last dose of AMG 420 after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20160370

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm / dd / yyyy

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
AMG 420				mm/dd/yyyy

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

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

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

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy ☐ Unknown

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

If N/A, date of termination (actual or planned) mm / dd / yyyy

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

If yes, provide date of delivery: mm / dd / yyyy

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

Print Form

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20160370

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
AMG 420				mm____/dd____/yyyy____

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

12.6 Appendix 6. Sample Storage and Destruction

Any blood, saliva, or bone marrow (BM) sample collected according to the Schedule of Activities (Section 2.2) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the multiple myeloma, the dose response and/or prediction of response to AMG 420, 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 [redacted] or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood, saliva, or BM 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 12.3 for subject confidentiality.

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

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

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

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

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

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, 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 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

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

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

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

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

If signs or symptoms recur with rechallenge, then Amgen investigational product is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate Case Report Form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 12.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a periossd 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.

12.8 Appendix 8. International Working Group Response Criteria for Multiple Myeloma (IMWG-URC)

Response criteria[a]	
Standard IMWG response criteria[b]	
sCR	• CR as defined below AND • Normal FLC ratio[c] AND • Absence of clonal cells in BM biopsy by immunohistochemistry κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells[d]
CR	• Negative immunofixation on the serum and urine AND • Disappearance of any soft tissue plasmacytomas AND • < 5% plasma cells in BM aspirates • In patients with baseline measurable disease only by sFLC, a normal FLC ratio is required
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis OR • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 hours • In patients with baseline measurable disease only by sFLC, a ≥ 90% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • In patients achieving a VGPR by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the SPD compared with baseline
PR	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours • In patients with baseline measurable disease only by sFLC, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline BM cell percentage was ≥ 30%. • If present at baseline, a ≥ 50% reduction in the size (SPD)[e] of soft tissue plasmacytomas is also required.
MR	• ≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hr urine M-protein by 50% to 89% • In patients with baseline measurable disease only by sFLC, a ≥25% but ≤ 49% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas (SPD)[e] is also required.
Stable disease	• Not recommended for use as an indicator of response • Stability of disease is best described by providing the time-to-progression estimates • Not meeting criteria for sCR, CR, VGPR, PR, minimal response, or PD

Footnotes are defined on last page of this table

Response criteria[a]	
Standard IMWG response criteria[b] (Continued)	
PD[f,g]	• Any 1 or more of the following criteria: – Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: – Serum M-protein (absolute increase must be ≥ 0.5 g/dL); o Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥ 5 g/dL; o Urine M-protein (absolute increase must be ≥ 200 mg/24 hr); o In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); – In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, BM plasma-cell percentage irrespective of baseline status (absolute increase must be ≥ 10%); – Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD[e] of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis; – ≥ 50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease
IMWG MRD criteria (requires a CR as defined above)	
Sustained MRD-negative	• MRD negativity in the marrow (NGS) and by imaging as defined below, confirmed minimum of 1 year apart. • Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)[h]
Sequencing MRD-negative	• Absence of clonal plasma cells by NGS on BM aspirate in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of BM aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[i] or higher
Imaging plus MRD-negative	• MRD negativity as defined by NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue[j]

Footnotes are defined on last page of this table

ASCT = autologous stem cell transplantation; BM = bone marrow; CR = complete response; CRAB features = calcium elevation, renal failure, anaemia, or lytic bone lesions; CT = computed tomography; FLC = free light chain; IMWG = International Myeloma Working Group; MR = minimal disease; MRD = minimal residual disease; MRI = magnetic resonance imaging; NGS = next generation sequencing; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; SPD = sum of the products of the maximal perpendicular diameters of measured lesions; SUV = standardized uptake value; VGPR = very good partial response

[a] All response categories require 2 consecutive assessments made any time before starting any new therapy; for MRD there is no need for 2 consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected CR. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

[b] Derived from international uniform response criteria for multiple myeloma. Minor response definition and clarifications derived from Rajkumar and colleagues. When the only method to measure disease is by serum FLC levels: CR can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the CR criteria listed previously. Very good PR in such patients requires a $\geq$ 90% decrease in the difference between involved and uninvolved FLC levels. All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

[c] All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

[d] Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of $>$ 4:1 or $<$ 1:2.

[e] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

[f] Positive immunofixation alone in a patient previously classified as achieving a CR will not be considered progression. For purposes of calculating time to progression and PFS, patients who have achieved a CR and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a CR or relapse from MRD should be used only when calculating disease-free survival.

[g] In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

[h] Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

[i] DNA sequencing assay on BM aspirate should use a validated assay such as LymphoSIGHT (Sequenta).

[j] Criteria used by Zamagni and colleagues, and expert panel (IMPetUs; Italian Myeloma criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least 2 consecutive slices. Alternatively, an $SUV_{max} = 2.5$ within osteolytic CT areas $>$ 1 cm in size, or $SUV_{max} = 1.5$ within osteolytic CT areas $\leq$ 1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by NGS.

Source: International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in MM (Kumar et al, 2016); modified for protocol purposes

12.9 Appendix 9. Clarification on Eligibility Criteria: Definition of Relapsed or Refractory Disease and Line of Treatment

Refractory multiple myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy: Nonresponsive disease is defined as either failure to achieve minimal response (MR). There are 2 categories of refractory multiple myeloma:

- **Relapsed and refractory multiple myeloma.** Relapsed and refractory multiple myeloma is defined as disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved MR or better at some point previously before then progressing in their disease course.
- **Primary refractory multiple myeloma.** Primary refractory multiple myeloma is defined as disease that is nonresponsive in patients who have never achieved a MR or better with any therapy. It includes patients who never achieve MR or better in whom there is no significant change in M-protein and no evidence of clinical progression as well as primary refractory, PD where patients meet criteria for true PD.

Relapsed multiple myeloma is defined as previously treated multiple myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either “primary refractory myeloma” or “relapsed-and-refractory multiple myeloma” categories.

A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner.

For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered 1 line of therapy (Rajkumar et al, 2011).

12.10 Appendix 10. Medications That May Cause QTc Prolongation

A list of medications known to cause QTc interval prolongation is available at the following link: https://crediblemeds.org/index.php/login/dlcheck

If a participant in this study does not have access to the internet, they can contact the institution investigational pharmacy or contact their study physician to obtain a list.

Table 12-3 presents a list of drugs that may prolong QTc. This is not an inclusive list of drugs and is provided for guidance only. The participant is encouraged to follow the list in this link above for the most up-to-date information. These drugs are prohibited during the study. Washout period is based on roughly 5 half-lives and rounded to a convenient interval. This list includes (but is not limited to) the following:

Table 12-3. Medications That May Cause QTc Prolongation

Compounds	Compound Half-Life	Possible Washout Period - Hours	Possible Washout Period - Days
Alfuzosin	~ 10 hours		7
Amantadine	17 ± 4 hours (10-25)		4
Amiodarone (cordarone)	58 days (15-142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	not characterized		
Azithromycin	40 hours		
Bepridil	42 hours (26-64)		10
Chloral hydrate	readily converted to trichloroethanol (active metabolite $T_{½}$ = 7-10 hours)	48	
Chloroquine	prolonged (days to weeks)		
Chlorpromazine	30 ± 7 hours		
Clarithromycin	non-linear PK 3-4 hours (250 mg Q12) 5-7 hours (500 mg Q12)	36	
Chloroquine	6-60 days; mean 20 days		
Desipramine*	> 24 hours, wide interpatient variability		
Disopyramide	6.7 hours (4-10)	36	
Dofetilide	10 hours	48	
Dolasetron	8.1 hours		
Domperidone	7-8 hours	48	
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	

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Table 12-3. Medications That May Cause QTc Prolongation

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
Erythromycin	*each salt form has different half-life*		
Felbamate	20-23 hours		5
Flecainide	20 hours (12-27)		5
Foscarnet	87.5 ± 41.8 hours *distribution and release from bone*		20
Fosphenytoin	12-29 hours		6
Gatifloxacin	7-14 hours	48	
Gemifloxacin	7 hours	48	
Grepafloxacin	16 hours		3
Halofantrine	6-10 days (variable among individual)		45
Haloperidol	18 ± 5 hours		5
Ibutilide	6 hours (2-12) *variable among subject*	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3
Isradipine	8 hours (multiple metabolites)	48	
Levofloxacin	6-8 hours	48	
Levomethadyl	multiple compartment PK with active metabolite 2.6 days for LAAM, 2 days for nor-LAAM, 4 days for dinor-LAAM		20
Lithium	24 hours (10-50)		7
Mesoridazine	24-48 hours (animal study)		10
Methadone	15-30 hours		7
Moexipril/HCTZ	2-9 hours (include active metabolite) for moexipril; 5.6-14.8 hours for HCTZ	48	
Moxifloxacin	12 ± 1.3 hours	72	
Naratriptan	6 hours	36	
Nicardipine	~ 2 hours post IV infusion	12	
Nortriptyline*	> 24 hours, wide interpatient variability		
Octreotide	1.7 hours	12	
Ofloxacin	5-7.5 hours		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)		1 to 3
Pentamidine	6.4 ± 1.3 hours	36	
Pimozide	55 hours		10

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Table 12-3. Medications That May Cause QTc Prolongation

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
Procainamide	3-4 hours for PA and NAPA (active metabolite)	24	
Protriptyline*	> 24 hours, wide interpatient variability		
Quetiapine	6 hours	36	
Quinidine	6-8 hours in adult; 3-4 hours in children	36	
Quinine	4-5 hours		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) $T_{½}$ = 21-30 hours (extensive to poor metabolizer)		4
Salmeterol	5.5 hours (only 1 datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16-30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~ 34 hours in healthy; ~ 19 hours in kidney transplant		7
Tamoxifen	5-7 days (biphasic)		30
Telithromycin	2-3 hours	24	
Thioridazine	20-40 hours (phenothiazines)		7
Tizanidine	2.5 hours	12	
Vardenafil	4-5 hours		
Venlafaxine	5 ± 2 hours for parent comp. 11 ± 2 hours for OVD (active metabolite)	60	
Voriconazole	6 hours; dose dependent		
Ziprasidone	7 hours	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	18	

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* Weakly associated with Torsades de pointes and/or QT prolongation, but that are unlikely to be a risk for Torsades de pointes when used in usual recommended dosages and in patients without other risk factors (eg, concomitant QT prolonged drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism).
Sources: Drug Facts and Comparison 2006, 2005; Physician's Desk Reference, 2002; Goodman & Gilman's the Pharmacological Basis of Therapeutics, 1996.

12.11 Appendix 11. Schedule of Activities in Case of Requirement for Dose Step

Table 12-4. Phase 1b Screening and Treatment Cycle 1 With Dose Step

	SCR	Treatment Period																												
Cycle		1																												Infusion-free Interval[a]
Cycle Day	-21 to -1	1									2	3	4									5	6	8	15	22	29		36
Hours		Pre-dose	Relative to start of infusion											Pre-step	Relative to start of infusion													EOI		
			0	1	2	4	6	8	12	16	20	24	48		0.5	1	2	4	6	8	12	16	20	24	48					
GENERAL AND SAFETY ASSESSMENTS																														
Informed consent	X																													
In-/Exclusion criteria	X																													
Demographics/Medical history	X																													
Hospitalization[b]		6 days																												
Concomitant medications	<---------- continually from informed consent until SFU ---------->																													
SAE review	<---------- continually from informed consent until SFU ---------->																													
AE review			<---------- continually from first dose of AMG 420 until SFU ---------->																												
Physical examination	X	X										X	X	X										X	X	X	X	X	X	X
Peripheral neuropathy	X																													
ECOG performance status	X	X																											X	
Height	X																													
Weight	X	X																												
Vital signs, pulse oximetry[c]	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement[c]	X	X										X	X	X										X	X				X	

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Table 12-4. Phase 1b Screening and Treatment Cycle 1 With Dose Step

	SCR	Treatment Period																												
Cycle		1																												Infusion-free Interval[a]
Cycle Day	-21 to -1	1										2	3	4									5	6	8	15	22	29		36
Hours		Pre-dose	Relative to start of infusion											Pre-step	Relative to start of infusion														EOI	
			0	1	2	4	6	8	12	16	20	24	48		0.5	1	2	4	6	8	12	16	20	24	48					
LABORATORY ASSESSMENTS																														
Pregnancy test[d]	X	X																												
Coagulation[e]	X	X						X				X	X	X						X				X	X	X	X	X	X	X
Hematology, chemistry[e]	X	X						X				X	X	X						X				X	X	X	X	X	X	X
Creatinine Clearance	X																													
Ferritin[f]		X	<---------- continue monitoring in case of CRS only ---------->																											
Hepatitis serology	X																													
Latent TB test	X																													
Urinalysis	X	X											X	X										X	X	X	X	X	X	X
Ig: IgA, IgM, IgG	X	X																												
[redacted]		[redacted]																												
PK ASSESSMENTS																														
AMG 420 PK collection[g]		X										X	X	X										X	X	X	X		X[g]	

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Table 12-4. Phase 1b Screening and Treatment Cycle 1 With Dose Step

	SCR	Treatment Period																														
Cycle		1																														Infusion-free Interval[a]
Cycle Day	-21 to -1	1										2	3	4																		36
Hours		Pre-dose	Relative to start of infusion											Pre-step	Relative to start of infusion																EOI	
			0	1	2	4	6	8	12	16	20	24	48		0.5	1	2	4	6	8	12	16	20	24	48							
DISEASE ASSESSMENTS																																
SPEP/SIFE[h]	X	X																												X		
UPEP/UIFE[h]	X	X																												X		
sβ-2 microglobulin	X																													X		
sFLC (κ/λ)	X	X																												X		
BM aspirate/biopsy[i]	X	At initial suspected CR and at 6 (after 4 cycles) months and repeat at 12 months for subjects who continue to appear to be in CR and recommended in case of PD/relapse																														
% MM involvement[i]	X	At initial suspected CR and at 6 (after 4 cycles) months and repeat at 12 months for subjects who continue to appear to be in CR and recommended in case of PD/relapse																														
BM FISH/karyotyping	X																															
Extramedullary plasmacytoma assessments[j]	X	<——— repeat only to confirm a PR or better only if measurable plasmacytoma present at baseline, every 12 weeks (± 2 weeks), as clinically indicated ———>																														
Skeletal survey[j]	X	<——— repeat only as clinically indicated ———>																														

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Table 12-4. Phase 1b Screening and Treatment Cycle 1 With Dose Step

	SCR	Treatment Period																												
Cycle		1																												Infusion-free Interval[a]
Cycle Day	-21 to -1	1										2	3	4										5	6	8	15	22	29	36
Hours		Pre-dose	Relative to start of infusion											Pre-step	Relative to start of infusion														EOI	
			0	1	2	4	6	8	12	16	20	24	48		0.5	1	2	4	6	8	12	16	20	24	48					
BIOMARKER ASSESSMENTS																														
[redacted]																														
INVESTIGATIONAL PRODUCT DOSING																														
AMG 420 cIV infusion			——————————————————————————>																											
Premedication[o]		X												X																

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Footnotes defined on next page
AE = adverse event; [redacted] cIV = continuous intravenous; CR = complete response; CRS = cytokine release syndrome; CT = computed tomography; [redacted] ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; FISH = fluorescent in situ hybridization; Ig = immunoglobulins; MDSCs = myeloid derived suppressor cells; MM = multiple myeloma; MRD = minimal residual disease; MRI = magnetic resonance imaging; [redacted] PD = progressive disease; PET = positron emission tomography; [redacted] PK = pharmacokinetics; PR = partial response; SAE = serious adverse event; [redacted] SCR = screening; sFLC (κ/λ) = serum free light chain (kappa/lambda); SFU = safety follow-up; SIFE = serum immunofixation; SPEP = serum protein electrophoresis; TB = tuberculosis; UIFE = urine immunofixation; UPEP = urine protein electrophoresis

[a] Infusion-free interval = days 30 to 42, day 43 = day 1 of subsequent cycle.

[b] See Section 7.1.1.4.1 for details on hospitalization requirements.

[c] ECGs and vital signs should be performed approximately 15 min prior to any invasive procedures including IV bag change, if applicable, and approximately 15 min prior to EOI. ECGs are only required in cycle 1 and 2.

[d] Refer to Section 9.2.4.1 for details of required pregnancy testing.

[e] As indicated in Section 12.2, hematology and chemistry panels include differential cell counts and comprehensive metabolic profile, as well as serum uric acid and phosphorous levels, and liver function tests. Coagulation panel includes prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and D-dimer.

[f] If ferritin value after CRS is abnormal, continue monitoring until values are back to baseline/event is resolved.

[g] Time schedule for PK sampling cycle 1 day 29: approximately 15 min prior to EOI and 4, 8, 24, and 48 hours after EOI.

[h] Serum and urine immunofixation (IFE) for M-protein measurements. Urine IFE to be followed up only if positive for M-protein at baseline.

[redacted]

[j] Baseline imaging is required at screening (if done within 30 days prior to screening for standard of care, no need to repeat) to evaluate for extramedullary (EM) relapse using whole body MRI or PET/CT and should be repeated during treatment only to confirm a PR or better only if measurable plasmacytoma are present at baseline every 12 weeks (± 2 weeks) and as clinically indicated. Skeletal survey does not need to be performed at screening if CT or PET-CT performed and does not need to be repeated after screening unless clinically indicated.

[k] MRD and [redacted]

[o] See Section 7.1.4 for details on premedication requirements.

12.12 Appendix 12. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 classifies tumor lysis syndrome (TLS) in grade 3 (present), grade 4 (life threatening consequences; urgent intervention indicated) and grade 5 (death). Presence of TLS is not clearly defined by CTCAE version 4.0. Cairo and Bishop developed a system for defining and grading TLS based on Hande-Garrow classification of laboratory or clinical TLS (Coiffier et al, 2008). For this trial the Cairo-Bishop classification will be used to define presence of TLS, ie, presence of laboratory TLS (see Table 12-5) and clinical TLS (see Table 12-6) including grading as detailed below.

Based on the Cairo and Bishop system, laboratory TLS is present when levels of 2 or more serum values of uric acid, potassium, phosphorus, or calcium are more than or less than normal at presentation or if they change by 25% within 3 days before or 7 days after initiation of treatment (Table 12-5).

Table 12-5. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (TLS)

Element	Value	Change from Baseline
Uric acid	≥ 476 μmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	25% increase
Phosphorus	≥ 2.1 mmol/L for children or ≥ 1.45 mmol/L for adults	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

Note: 2 or more laboratory changes within 3 days before or 7 days after cytotoxic therapy will constitute laboratory TLS.

Clinical TLS requires the presence of laboratory TLS in addition to 1 or more of the following significant complications: renal insufficiency, cardiac arrhythmias/sudden death, and seizures (Table 12-6). The grade of clinical TLS is defined by the maximal grade of the clinical manifestations as detailed in Table 12-6.

Table 12-6. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

Grade	Creatinine[a, b]	Cardiac Arrhythmia[a]	Seizure[a]
0	≤ 1.5 x ULN	n1	n1
1	1.5 x ULN	intervention not indicated	--
2	> 1.5 – 3.0 x ULN	non urgent medical intervention indicated	one brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL
3	> 3.0 – 6.0 x ULN	symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention
4	> 6.0 x ULN	life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)
5	Death	death	death

Note: Laboratory TLS and at least 1 clinical complication will constitute clinical TLS.
ADL = activities of daily living; CHF = congestive heart failure; TLS = tumor lysis syndrome; ULN = upper limit of normal
[a] not directly or probably attributable to therapeutic agent
[b] if no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: > 1 to < 12 years of age, both male and female, 61.6 μmol/L; ≥ 12 to < 16 years, both male and female, 88 μmol/L; ≥ 16 years, female 105.6 μmol/L, male 114.4 μmol/L

12.13 Appendix 13. Performance Status According to Eastern Cooperative Oncology Group (ECOG) 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

12.14 Appendix 14. Protocol-specific Anticipated Serious Adverse Events

Anticipated serious adverse events are events that are anticipated to occur in the study population at some frequency independent of investigational product exposure and do not need to be reported individually as a Food and Drug Administation (FDA) Investigational New Drug (IND) safety report by the sponsor. Identification and reporting of anticipated serious adverse events is the responsibility of the sponsor; the investigator is responsible for reporting adverse events and serious adverse events as described in Section 12.4.

Table 12-7. Anticipated Serious Adverse Events for Study 20160370

Preferred Term[a]	Preferred Term[a]
anaemia	immunoglobulin level increased
anaemia of malignant disease	infection in an immunocompromised host
back pain	leukopenia
blood albumin abnormal	malaise
blood albumin decreased	nephrotic syndrome
blood albumin increased	neutropenia
blood calcium increased	oliguria
bone pain	osteopenia
chronic kidney disease	osteoporosis
creatinine increased	pain in extremity
electrophoresis abnormal	plasma cell myeloma
electrophoresis protein abnormal	plasma cell myeloma recurrent
end stage renal disease	plasmacytoma
fatigue	pathological fracture
fracture	platelet count decreased
hemoglobin decrease	protein total increased
hyperalbuminemia	renal failure
hypercalcemia	skeletal pain
hypercalcemia of malignancy	thrombocytopenia
hyperproteinaemia	urine electrophoresis abnormal
hyperviscosity syndrome	venous thrombosis
hypoalbuminaemia	white blood cell count decreased
immunoglobulin level decreased	

[a] MedDRA Version 21

12.15 Appendix 15. Peripheral Neuropathy Assessment

TNSr Items	0	1	2	3	4
Symptom extension (tingling, numbness, neuropathic pain)[a]	none	symptoms limited to fingers or toes	symptoms extend to ankle or wrist	symptoms extend to knee or elbow	symptoms above knees or elbows or functionally disability
Pin sensibility	normal	reduced in fingers/toes	reduced up to wrist/ankle	reduced up to elbow/knee	reduced up to above elbow/knee
Vibration sensibility	normal	reduced in fingers/toes	reduced up to wrist/ankle	reduced up to elbow/knee	reduced up to above elbow/knee
Strength[b]	normal	mild weakness	moderate weakness	severe weakness	paralysis
Tendon reflexes	normal	ankle reflex reduced	ankle reflex absent	ankle reflex absent/others reduced	all reflexes absent

TNSr = total neuropathy score-reduced
[a] The worse score of the 3 subcomponents (tingling/paresthesia, numbness, and neuropathic pain proximal extension) was used as the subjective symptom extension score.
[b] The muscle with the worse score is used as the strength score (toe, ankle, wrist and finger extensors and flexors, quadriceps, hamstrings, biceps, and triceps). TNSr and pain items were adapted with permission (Smith et al, 2010).

Amendment 5

Protocol Title: A Phase 1b Multicenter, Open-label, Expansion Study to Assess the Safety and Efficacy of AMG 420 in Subjects With Relapsed and/or Refractory Multiple Myeloma

Amgen Protocol Number AMG 420 20160370

Amendment Date: 17 September 2021

Rationale:

The rationale for this protocol amendment are:

- To put clarifications around delays of treatment cycles in place (Section 7.1.1.2, 7.4.2.1.2.2 and 9.1.2)
- To add clarity around treatment free intervals (Section 7.1.1.3)
- To remove second course treatment in the protocol as it is no longer warranted for study conduct due to termination of the program and no further supply of AMG 420 (Section 5.1.1, 6.2, 7.4.2.1.3, 9.1.3, 10.2.1, and Appendix 13)
- To add table for management of COVID infection (Section 7.4.2.1.2.4)
- To add SARS-COV-9 vaccination criteria under Section 7.1.8
- Several sections of the protocol have been updated to include required alignments with current Amgen protocol template (Sections 2.2, 7.1.6, 9.2.3.1.1.2, 9.2.3.1.1.3, 12.2, 12.3, and 12.4).
- Administrative and editorial changes (including grammatical, typographical, and formatting) have been made throughout the protocol.

Amendment 4

Protocol Title: A Phase 1b Multicenter, Open-label, Expansion Study to Assess the Safety and Efficacy of AMG 420 in Subjects With Relapsed and/or Refractory Multiple Myeloma

Amgen Protocol Number (AMG 420) 20160370

NCT Number: NCT03836053

Amendment 4 Date: 20 May 2020

Rationale:

This protocol was amended to address the following:

- Removal of Phase 1b Part 2 (combination cohort) and Phase 2 text globally
- Updated restart guidance after adverse event to correct inconsistency within Table 7-5

Amendment 3

Protocol Title: A Phase 1b/2 Multicenter, Open-label, Expansion Study to Assess the Safety and Efficacy of AMG 420 in Subjects With Relapsed and/or Refractory Multiple Myeloma (ParadigMM-1A)

Amgen Protocol Number (AMG 420) 20160370

NCT Number: NCT03836053

Amendment Date: 22 May 2019

Rationale:

This protocol is being amended to:

- Include new phase 1b part 2 combination cohort [redacted], maximum 20 additional subjects to be enrolled in this cohort).
- Addition of adverse event management guidance for phase 2 study, including dose reduction and discontinuation parameters for discrete event occurring on treatment.
- Changes made to clarify guidance on infusion reactions and tumor lysis syndrome.
- Adjustment made to platelet count eligibility criteria.
- Addition of patient interviews for phase 1b study and patient reported outcome measurement tools to phase 2 study.
- Updated timing of imaging assessments for extramedullary disease, providing option for multiple assessments while responders remain on treatment.
- Updated statement of hypothesis added and revisions to statistical analysis plan (Section 10) made to provide sample size justification for the phase 2 study.
- Change primary analysis time point.
- Remove expired Amgen template language to ensure compliance with current Amgen template, including removal of disease related events as a subcategory of adverse events.

Amendment 2

Title: A Phase 1b/2 Multicenter, Open-label, Expansion Study to Assess the Safety and Efficacy of AMG 420 as Monotherapy in Subjects With Relapsed and/or Refractory Multiple Myeloma

AMG 420

Amgen Protocol Number 20160370

IND number BB-IND 134608

Amendment Date: 12-December-2018

Rationale:

This protocol is being amended based on comments received from the FDA during a Type C meeting, and also to align with changes to the protocol for the BI 836909 FIH trial.

The following changes were made to Protocol Amendment 1, dated 11 October 2018:

- Inclusion Criteria # 103 was modified to incorporate FDA feedback on:
  - The requirement for subjects to be relapsed and/or refractory to ≥ 3 lines of therapy which must include a CD38-directed monoclonal antibody.
  - The inclusion of subjects who could not tolerate PIs, IMiDs, or CD38-directed monoclonal antibody.

- Language added regarding management of patients who develop fevers during treatment with AMG 420
- The table of contents and all references are updated accordingly.

Amendment 1

Title: A Phase 1b/2 Multicenter, Open-label, Expansion Study to Assess the Safety and Efficacy of AMG 420 as Monotherapy in Subjects With Relapsed and/or Refractory Multiple Myeloma

AMG 420

Amgen Protocol Number 20160370

IND number BB-IND 134608

Amendment Date: 11-October-2018

Rationale: This protocol is being amended based on comments received from the FDA upon submission of the US IND on August 31, 2018. All updates are in line with changes requested by the agency.

The following changes were made to the original protocol, dated 15 August 2018:

- DLT criteria was revised to specify the grade and time to resolution for the DLT exceptions of headache, insomnia, and fever.
- Removed exclusion for Grade 3 neurological events tht improve to Grade 0 or Grade 1 within 14 days from DLT evaluation
- Clarification added to indicate mandatory dose interruption for Grade 4 adverse events (AMG 420 related or non-related) and restart after improvement of the toxicity to a specified lower grade.
- Incorporated Phase 2 stopping rules that apply to Grade 4 or higher drug-related adverse events, excluding lymphopenia (or reduced lymphocyte counts).
- Stopping rules for Phase 2 adjusted to be applied by the DRT after every 20 subjects have had the chance to receive at least 1 cycle of treatment at the determined dose level.
- Clarifications/minor corrections for consistency throughout protocol
- Clarifications/minor corrections to Schedule of Assessments
- The table of contents and all references are updated accordingly.