Title Page

Protocol Title:		A Global Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of the Half-life Extended Bispecific T-cell Engager AMG 910 in Subjects With Claudin 18.2-Positive Gastric and Gastroesophageal Junction Adenocarcinoma
Short Protocol Title:		A Phase 1 Study of AMG 910 in Subjects with CLDN18.2-Positive Gastric and Gastroesophageal Junction Adenocarcinoma
Protocol Number:		20180292
Investigational Product:		AMG 910
Trade Name:		Not applicable
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Data Elements 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 entitled A Global Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of the Half-life Extended Bispecific T-cell Engager AMG 910 in Subjects With Claudin 18.2-Positive Gastric and Gastroesophageal Junction Adenocarcinoma, dated **02 March 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)

Table of Contents

List of Tables

List of Figures

1. Protocol Summary

1.1 Synopsis

Protocol Title: A Global Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of the Half-life Extended Bispecific T-cell Engager AMG 910 in Subjects With Claudin 18.2-Positive Gastric and Gastroesophageal Junction Adenocarcinoma

Short Protocol Title: A Phase 1 Study of AMG 910 in Subjects with CLDN18.2-Positive Gastric and Gastroesophageal Junction Adenocarcinoma

Study Phase: 1

Indication: Gastric and Gastroesophageal Junction Adenocarcinoma

Rationale

Combining a highly selective therapeutic target with a T cell-mediated killing mechanism has been shown to constitute an effective anticancer treatment. AMG 910 is a novel half-life extended (HLE) bispecific T cell engager (BiTE®) molecule designed to direct T cells towards Claudin**-**18 **isoform** 2 (CLDN18.2)-expressing cells. The pharmacological effect of AMG 910 is mediated by redirection of cytotoxic CD8+ or CD4+ T lymphocytes to kill CLDN18.2-expressing cells and the cytotoxic potency was demonstrated in in vitro and in vivo experiments. Based on its mechanism of action, nonclinical data, and clinical experience, both with CLDN18.2-targeting drugs and with an approved BiTE therapy, AMG 910 may address an unmet need for patients with gastric and gastroesophageal junction (GEJ) cancer.

This is a first-in-human study in adult subjects with CLDN18.2-positive gastric or GEJ adenocarcinoma, collectively referred to as “gastric cancer” in this clinical investigation to assess the safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of AMG 910, with additional exploratory objectives to [redacted]

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of AMG 910 in adult subjects • To determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D)	• Dose-limiting toxicities (DLT) • Treatment-emergent adverse events • Treatment-related adverse events • Changes in vital signs, electrocardiogram (ECG), and clinical laboratory tests

Objectives	Endpoints
Secondary	
• To characterize the PK of AMG 910	• PK parameters for AMG 910 following **short-term** intravenous (IV) **and extended IV (eIV)** administration including but not limited to maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), area

	under the concentration-time curve (AUC) over the dosing interval, accumulation following multiple dosing, and, if feasible, half-life ($t_{1/2}$)
• To evaluate preliminary anti-tumor activity of AMG 910	• Objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and iRECIST • Duration of response (DOR) • Time to progression • Progression-free survival (PFS), 6-month and 1-year PFS • Overall survival (OS), 1 and 2-year OS

Overall Design

This is an open-label, ascending, multiple dose, phase 1 study evaluating AMG 910 in subjects with CLDN18.2-positive gastric and GEJ adenocarcinoma. The study will consist of:

- Dose-exploration phase
- Dose-expansion phase

The dose-exploration phase of the study will estimate the MTD of AMG 910 using a Bayesian logistic regression model (BLRM). A RP2D may be identified based on emerging safety, efficacy, and pharmacodynamic data prior to reaching an MTD. Following the dose-exploration phase, a dose-expansion phase will be conducted to confirm safety, PK, and pharmacodynamics at the MTD or RP2D and to obtain further safety and efficacy data and enable correlative biomarker analysis.

Because of the observation of cytokine release syndrome (CRS) events in cohort 1, the dosing of AMG 910 and the dose escalation schedule will be adapted and AMG 910 will be administered in cycle 1 week 1 as an extended intravenous (IV) infusion (eIV) for 96 hours starting on day 1 followed by weekly short-term IV infusions (approximately 60 minutes) for all cycles of subjects enrolled in next cohorts (cohorts 1b and beyond).

Number of Subjects

Approximately 70 subjects will be enrolled in this study.

Summary of Subject Eligibility Criteria

Key Inclusion Criteria:

- Subjects with histologically or cytologically confirmed metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma positive for CLDN18.2 as defined by the test described herein (Section 8.2.10.1). Prior treatment with any CLDN18.2-targeting product requires testing of a tissue sample obtained after the treatment with the CLDN18.2-targeting product (not applicable for re-treatment with AMG 910).

- Subjects should not be eligible for curative surgery and should have been refractory to or have relapsed after 2 or more prior lines of standard systemic therapy that included a platinum, a fluoropyrimidine, either a taxane or irinotecan, and an approved vascular endothelial growth factor receptor (VEGFR) antibody/tyrosine kinase inhibitor (TKI) **and depending on country-specific standards and approvals**.
- For subjects eligible for human epidermal growth factor receptor 2 (HER2) directed therapy, prior systemic therapy should have included a HER2 targeting antibody approved for treatment of gastric cancer.
- Subjects may also be included if the aforementioned therapeutic options were medically not appropriate for them. In these cases, the reason(s) why required prior therapies for gastric cancer were medically not appropriate should be documented in the subject's electronic case report form (eCRF).
- For dose-expansion only: Subjects with at least 1 measurable lesion ≥ 10mm which has not undergone biopsy within 3 months of screening scan. This lesion cannot be biopsied at any time during the study.

Key Exclusion Criteria:

- Any anticancer therapy or immunotherapy within 4 weeks of start of first dose **(14 days for palliative radiation)**.
- Untreated or symptomatic central nervous system (CNS) metastases, leptomeningeal disease, or spinal cord compression.
- Autoimmune disorders requiring chronic systemic steroid therapy or any other form of immunosuppressive therapy while on study, eg, ulcerative colitis, Crohn's disease, or any other gastrointestinal autoimmune disorder causing chronic nausea, vomiting, or diarrhea. Recent or current use of inhaled steroids or physiological substitution in case of adrenal insufficiency is not exclusionary.
- Evidence or history within last 3 months of gastrointestinal inflammatory conditions not associated with the underlying cancer disease including gastrinomas, duodenitis, proven gastric ulcer, duodenal ulcer, pancreatitis, or subjects with recent gastric bleeding. Subjects may be included if the symptomatic/immunosuppressive treatment is discontinued more than 4 weeks prior to the first dose of AMG 910, symptoms have resolved, and gastroscopy does not indicate signs of active disease.

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

Treatments

Investigational product (AMG 910) will be administered as a short-term IV infusion (approximately 60 minutes) or as extended IV (eIV) infusion over 96 hours (in cycle 1 week 1) over six 28-day cycles following the doses and dosing schedule outlined in Table 6-2 and Section 6.1. There will be treatment-free intervals of 2 weeks after cycles 2 and 4. There will be no further scheduled treatment interruptions between any other cycles.

The following premedication may be used:

Dexamethasone and a proton pump inhibitor may be used as prophylactic measures before each infusion as defined in Section 6.1.4.

Procedures

After written informed consent has been obtained, all screening tests and procedures will be performed within 21 days prior to cycle 1 day 1 dosing, unless otherwise noted. Serial clinical safety and study evaluations as per the Schedule of Activities **(SoA)** will be performed including physical examination, vital signs, clinical laboratory tests, radiological assessment, PK, anti-drug antibody and biomarker sample collections. All subjects will receive baseline assessment by contrast-enhanced computed tomography (CT) scan before dosing. Endoscopic evaluation of the upper digestive system including esophagus, stomach and first part of the small intestine according to local standards will be done as scheduled in Table 1-1 and after occurrence of toxicity observations as detailed in Table 6-3 (eg, pain in the upper abdomen, vomiting, bleeding).

All subjects will be hospitalized for intensive monitoring for 4 days of eIV infusion in days 1 to 5 of cycle 1 week 1 and for 48 hours after dosing on day 8, and for 24 hours after weekly short-term IV dosing on days 15 and 22 (days 10, 15, 17, 22, and 24 in a twice-weekly short-term IV dosing schedule) during the first cycle and day 1 during the third cycle. Subjects may be discharged after this period if there are no grade ≥ 2 adverse events at least possibly related to AMG 910. Minimum hospitalization times for subjects are described in detail in Table 6-1. For all dosing visits that do not require hospitalization, subjects will be intensely monitored for an observation period of at least 4 hours after end of each AMG 910 infusion in cycles 2 through 6 and for 8 hours after end of infusion (EOI) on cycle 3 day 8.

Routine radiological imaging (contrast-enhanced CT scans) and tumor burden assessments will be performed as outlined in the Schedule of Activities. Assessment of disease response will be determined based on RECIST 1.1 and iRECIST guidelines.

To further assess the risk of delayed adverse events, the subject must return for a safety follow-up visit at least 30 (+3) days after the last dose of AMG 910. Long-term follow-up will be conducted every 6 months up to 2 years from the first dose of AMG 910 by clinic visit, telephone, chart review or by access of public databases to assess for survival, serious adverse events, and/or the commencement of subsequent cancer therapy for all subjects who have not withdrawn consent. **Subjects who remain on the treatment for more than 2 years do not need to have additional long-term follow-up. They will complete the study 30 (+3) days following discontinuing treatment.**

For a full list of study procedures, including the timing of each procedure, please refer to Section 8.2 and the Schedule of Activities in Table 1-1.

Statistical Considerations

All subjects who are enrolled and receive at least 1 dose of AMG 910 will be included in the analysis, unless otherwise specified. A formal interim analysis of available safety and efficacy data will occur when all dose-escalation subjects have had the opportunity to complete 28 days on study. This interim analysis will estimate the MTD, support the determination of the RP2D, and support the evaluation of the benefit/risk profile of AMG 910.

The primary analysis for the safety endpoints, PK endpoints, and objective response endpoints will occur when enrollment is complete, and each subject has had the opportunity to receive at least 6 cycles of treatment. The primary analysis for time to event endpoints will occur when enrollment is complete, and each subject has had the opportunity to be on the study for at least 2 years. The final analysis will occur when target enrollment is complete for both phases and all subjects have ended the study.

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

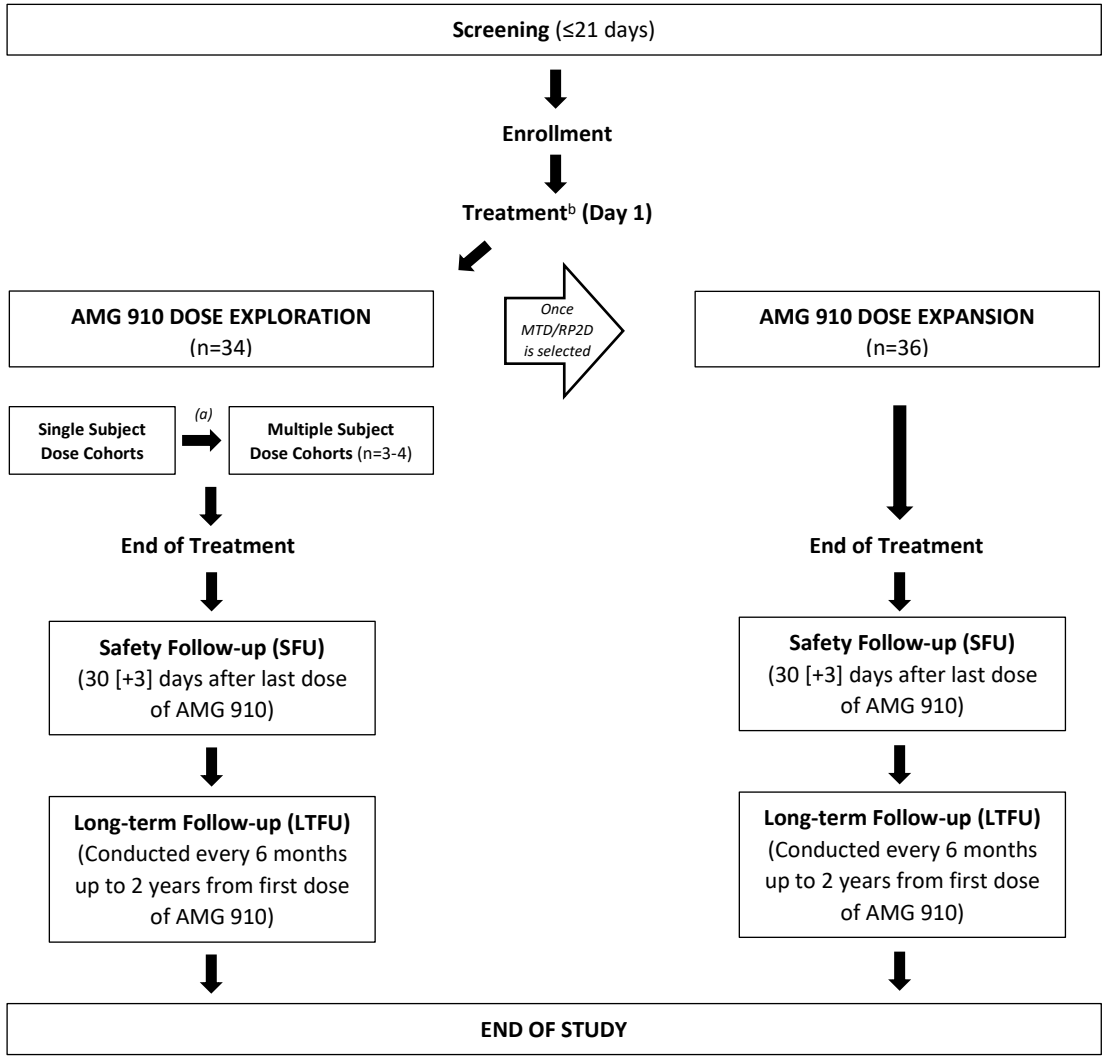
Statistical Hypotheses

AMG 910 will demonstrate acceptable safety and tolerability in subjects with gastric or GEJ adenocarcinoma at 1 or more dose levels with at least 1 dose level showing evidence of anti-tumor activity.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1. Study Schema



CT = computed tomography; **IV = intravenous; LTFU = long-term follow-up;** MRI = magnetic resonance imaging; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose; SCR = screening; SFU = safety follow-up

[a] Multiple-subject cohorts will enroll at a dose level where specific safety and/or efficacy criteria were met in a single-subject cohort or per planned dose level from Table 6-2. For subsequent dose level cohorts, 3-4 total subjects will be enrolled.

[b] **For cohorts 1b onwards, AMG 910 is administered as extended IV infusion over 96 hours in cycle 1 week 1 and as short-term IV infusions weekly (or twice weekly) starting cycle 1 day 8 onwards in cycle 1 through 6 of 28-day cycles with scheduled 2-week breaks after cycles 2 and 4 (see Section 6).**

Note: For SCR CT and/or MRI, allowing 30 days from C1D1.

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities

	SCR[a]	Treatment Cycle 1																																					
Week		1							2											3										4									
Cycle Day		1			2	3	4	5	8				9	10					11	15				16	17				18	22				23	24				25
Hour (relative to EOI[b])		PRE	0	**6**	24	**48**	**72**	**96 EOI**	PRE	0	EOI	4	24	**48**	PRE	0	EOI	4	24	PRE	0	EOI	4	24	PRE	0	EOI	4	24	PRE	0	EOI	4	24	PRE	0	EOI	4	24
GENERAL AND SAFETY ASSESSMENTS																																							
Informed consent	X																																						
Clinical evaluation[c]	X	X			X	X	X	X	X				X	**X**	X[o]				X[o]	X				X	X[o]				X[o]	X				X	X[o]				X[o]
Vital signs, pulse oximetry	X	X		X[d]		X		X	X		X[d]				X[o]		X[d,o]			X		X[d]			X[o]		X[d,o]			X		X[d]			X[o]		X[d,o]		
12-lead ECG[e] triplicate	X	X				**X**			X		X				X[o]		X[o]					X					**X**[o]					X					X[o]		
Adverse events review	Continually throughout study																																						
Serious adverse events review	Continually throughout study																																						
Prior/concomitant medication	Continually throughout study																																						
LOCAL LABORATORY ASSESSMENTS																																							
Pregnancy test[f]	X	X																																					
HIV, Hepatitis B and C screening	X																																						
CBC with differential	X	X			X	X	X	**X**	X			X	X	**X**	X[o]			X[o]	X[o]	X				X	X[o]				X[o]	X				X	X[o]				X[o]
Coagulation	X	X			X	X	X	**X**	X			X	X	**X**	X[o]			X[o]	X[o]	X				X	X[o]				X[o]	X				X	X[o]				X[o]
Chemistry panel	X	X			X	X	X	**X**	X			X	X	**X**	X[o]			X[o]	X[o]	X				X	X[o]				X[o]	X				X	X[o]				X[o]
Urinalysis	X																			**X**																			
OTHER ASSESSMENTS/PROCEDURES																																							
Gastroscopy[g]	X[g]																																						
CENTRAL LABORATORY ASSESSMENTS																																							
[redacted]																																							
STUDY TREATMENT AND OTHER ASSESSMENTS / PROCEDURES																																							
Imaging	See Table 1-3 - imaging assessments																																						
AMG 910 extended IV (eIV) infusion		**X**																																					
AMG 910 short-**term** IV infusion										X						**X**[o]					X					**X**[o]					X					**X**[o]			
Hospital stay		From day 1 until **4** hours after EOI on day **5.**							Until 48 hours after EOI on day 8. **-OR- Until 48 hours after EOI on day 8 and until 24 hours after EOI on day 10[o].**											Until 24 hours after EOI on day 15.					Until 24 hours after EOI on day 17[o].					Until 24 hours after EOI on day 22.					Until 24 hours after EOI on day 24[o].				

Abbreviations and footnotes defined on last page of table

Page 1 of 5

Table 1-1. Schedule of Activities

	Treatment Cycle 2[l]																															
Week	1								2								3								4							
Cycle Day	1				3				8				10				15				17				22				24			
Hour (relative to EOI[b])	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4
GENERAL AND SAFETY ASSESSMENTS																																
Clinical evaluation[c]	X			X	Xº			Xº	X			X	Xº			Xº	X			X	Xº			Xº	X			X	Xº			Xº
Vital signs, pulse oximetry	X		X[d]		Xº		X[d,o]		X		X[d]		Xº		X[d,o]		X		X[d]		Xº		X[d,o]		X		X[d]		Xº		X[d,o]	
12-lead ECG[e]	X																															
Adverse events review	Continually throughout study																															
Serious adverse events review	Continually throughout study																															
Prior/concomitant medication	Continually throughout study																															
LOCAL LABORATORY ASSESSMENTS																																
Pregnancy test[f]	X																															
CBC with differential	X			X	Xº			Xº	X			X	Xº			Xº	X			X	Xº			Xº	X			X	Xº			Xº
Coagulation	X			X	Xº			Xº	X			X	Xº			Xº	X			X	Xº			Xº	X			X	Xº			Xº
Chemistry panel	X			X	Xº			Xº	X			X	Xº			Xº	X			X	Xº			Xº	X			X	Xº			Xº
Urinalysis					Xº													X														
OTHER ASSESSMENTS/PROCEDURES																																
Gastroscopy[g]													Xg																			
CENTRAL LABORATORY ASSESSMENTS																																
[redacted]																																
STUDY TREATMENT AND OTHER ASSESSMENTS / PROCEDURES																																
Imaging	See Table 1-3 - imaging assessments																															
AMG 910 short-term IV infusion		X				Xº				X				Xº				X				Xº				X				Xº		
Observation	Until 4 hours after EOI on day 1				Until 4 hours after EOI on day 3º				Until 4 hours after EOI on day 8				Until 4 hours after EOI on day 10º				Until 4 hours after EOI on day 15				Until 4 hours after EOI on day 17º				Until 4 hours after EOI on day 22				Until 4 hours after EOI on day 24º			

Abbreviations and footnotes defined on last page of table

Table 1-1. Schedule of Activities

	Treatment Cycle 3																
Week	1					2				3				4			
Cycle Day	1				2	8				15				22			
Hour (relative to EOI[b])	PRE	0	EOI	4	24	PRE	0	EOI	8	PRE	0	EOI	4	PRE	0	EOI	4
GENERAL AND SAFETY ASSESSMENTS																	
Clinical evaluation[c]	X			X	X	X			X	X			X	X			X
Vital signs, pulse oximetry	X		X[d]			X		X[d]		X			X	X			X
12-lead ECG[e]	X																
Adverse events review	Continually throughout study																
Serious adverse events review	Continually throughout study																
Prior/concomitant medication	Continually throughout study																
LOCAL LABORATORY ASSESSMENTS																	
Pregnancy test[f]	X																
CBC with differential	X			X		X			X	X			X	X			X
Coagulation	X			X		X			X	X			X	X			X
Chemistry panel	X			X		X			X	X			X	X			X
Urinalysis	X									X							
CENTRAL LABORATORY ASSESSMENTS																	
[redacted]																	
STUDY TREATMENT AND OTHER ASSESSMENTS / PROCEDURES																	
Imaging	See Table 1-3 - imaging assessments																
AMG 910 short-term IV infusion		X					X				X				X		
Hospital Stay (Day 1 only)	Until 24 hours after EOI on day 1																
Observation						Until 8 hours after EOI on day 8				Until 4 hours after EOI on day 15				Until 4 hours after EOI on day 22			

Abbreviations and footnotes defined on last page of table

Table 1-1. Schedule of Activities

	Treatment Cycles 4 through 6[l]																EOT[j]	SFU	LTFU
Week	1				2				3				4						
Cycle Day	1				8				15				22				28		
Hour (relative to EOI[b])	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4			
GENERAL AND SAFETY ASSESSMENTS																			
Clinical evaluation[c]	X			X	X			X	X			X	X			X	X	X	
Vital signs, pulse oximetry	X			X	X			X	X			X	X			X	X	X	
12-lead ECG[e]	X																		
Adverse events review	Continually throughout study																		
Serious adverse events review	Continually throughout study																		**X**
Prior/concomitant medication	Continually throughout study																		
Survival Status and/or subsequent cancer therapy																			X
LOCAL LABORATORY ASSESSMENTS[n]																			
Pregnancy test[f]	X																	X	
CBC with differential	X			X	X			X	X			X	X			X	X	X	
Coagulation	X			X	X			X	X			X	X			X	X	X	
Chemistry panel	X			X	X			X	X			X	X			X	X	X	
Urinalysis	X								X										
CENTRAL LABORATORY ASSESSMENTS																			
[redacted]																			
STUDY TREATMENT AND OTHER ASSESSMENTS / PROCEDURES																			
Imaging	See Table 1-3 - imaging assessments																		
AMG 910 short-term IV infusion		X				X				X				X					
Observation	Until 4 hours after EOI on day 1				Until 4 hours after EOI on day 8				Until 4 hours after EOI on day 15				Until 4 hours after EOI on day 22						

Abbreviations and footnotes defined on last page of table

Table 1-1. Schedule of Activities

	Treatment-free Intervals after Cycles 2 and 4 (2 weeks)[m]	
Week	1	2
Day[k] (out of 14-day treatment-free interval)	1	8
GENERAL AND SAFETY ASSESSMENTS		
Clinical evaluation[c]	X	X
Vital signs, pulse oximetry	X	X
Adverse events review	Continually throughout study	
Serious adverse events review	Continually throughout study	
Prior/concomitant medication	Continually throughout study	
LOCAL LABORATORY ASSESSMENTS		
CBC with differential	X	X
Coagulation	X	X
Chemistry panel	X	X
Urinalysis	X	
OTHER ASSESSMENTS / PROCEDURES		
Imaging	See Table 1-3 - imaging assessments	

Page 5 of 5

AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; EOI = end of infusion; EOT = end of treatment; IV = intravenous; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; Pre = pre-infusion; SAE = serious adverse event; SCR = screening; SFU = safety follow-up; ctDNA = circulating tumor DNA; PB = peripheral blood

[a] All screening procedures should be performed within 21 days prior to cycle 1 day 1 dosing if not stated differently in Section 8.1.1.

[b] End of Infusion (EOI) is considered as the end of the controlled rate post-infusion flush.

[c] Clinical evaluation including physical exam, ECOG, weight, and neurological examination (as described in Section 8.2.1.5). Performed at Screening only: demographics, medical history, and height.

[d] Refer to Section 8.2.3.1 and Section 8.2.3.2 for additional vital sign and pulse oximetry collection time points.

[e] Triplicate ECGs to be collected at Screening and in cycle 1 only. Single ECGs will be collected per time point for cycle 2 and beyond. Refer to Section 8.2.3.3.

[f] Pregnancy testing is required for all female subjects of childbearing potential. Serum pregnancy test at Screening and within 48 hours prior to first dose of AMG 910. Beginning with cycle 2 and beyond, within 48 hours of start of each following cycle during treatment with protocol-required therapies or at monthly intervals thereafter until 75 days after the last dose of protocol-required therapies.

[redacted]

[j] EOT visit will take place on cycle 6 day 28 (± 2 days) **for subjects that completed 6 cycles or on the day that subject is unable to continue study treatment (early termination)**.

[k] Visits during the 14-day treatment-free intervals will be completed on the first day of each week (± 2 days).

[l] After cycles 2 and 4, refer to page 3 of Table 1-1 for assessments performed during the **2**-week treatment-free intervals.

[m] There will be planned treatment-free intervals of 2 weeks after cycles 2 and 4. This may be extended up to 3 weeks for reasons described in Section 4.1. If there is a **third** week of observation, the same assessments are to be performed on day 15 as on days 1 and 8 of the treatment-free interval.

[n] Laboratory assessments that were done within 24 hours prior to infusion do not need to be repeated.

º Only applies to twice weekly dosing schedule.

Table 1-2. Schedule of Pharmacokinetic Samples[a]

		Hours after **start** of infusion								
	Pre-infusion	1	2	4	24	48	**72**	**96**	**120**	**144**
Cycle 1 (day 1 **to day 7**)	X	X	X	X	X	**X**	**X**	**X**	**X[b]**	**X[b]**
	Pre-infusion	**End of infusion (EOI[c])**	**Hours after end of infusion**							
			2	4	24					
Cycle 1 (days 8 and 10[d])	X	X		X	X					
Cycle 1 (days 15, 17[d], and 22)	X	X								
Cycle 1 (day 24)[d]	X	X	X	X	X					
Cycle 2 (days 1, 3[d], 8, 10[d], 15, 17[d], and 22)	X	X								
Cycle 2 (day 24)[d]	X	X	X	X						
Cycle 3 (day 1)	X	X	X	X	X					
Cycle 3 (days 8, 15, and 22)	X	X								
Cycle 4, 5, and 6 (day 1)	X	X								

[a] Pharmacokinetic (PK) samples should be collected at the exact nominal time point as noted. If unable to collect a PK sample at the specified nominal time point collect it as close as possible to the nominal time point and record the actual collection time. Pharmacokinetic samples collected ± 15 minutes from planned nominal time point will not be considered protocol deviations. **Sample collection should be peripheral access (collection from central line/port should be avoided).**

[b] **This sample will only be collected if the patient is hospitalized at the time.**

[c] End of Infusion (EOI) is considered as the end of the controlled rate post-infusion flush.

[d] **Only applies to twice-weekly dosing schedule when AMG 910 weekly dosing demonstrates acceptable safety and tolerability in subjects with gastric or gastroesophageal junction (GEJ) adenocarcinoma at 1 or more dose levels with at least 1 dose level showing evidence of anti-tumor activity.**

Table 1-3. Schedule of Imaging Assessments (Cycle Independent)

	SCR	Treatment Period	EOT	SFU	LTFU	Notes
MRI brain	X					All subjects must have MRI of the brain performed within 21 days prior to the first dose of AMG 910. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain can be performed at any time if clinically indicated per standard of care
Contrast enhanced CT and tumor burden[a] assessment[b]	X	• Every 6 weeks for first 12 weeks • Every 8 weeks thereafter	X	X	X[a]	Radiologic imaging (CT) is required at the EOT or SFU visit if the subject has not had radiologic imaging performed within 8 weeks of the visit.

CT = computed tomography; EOT = end of treatment; ICF = Informed Consent Form; LTFU = long-term follow-up; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; iRECIST = immune Response Evaluation Criteria in Solid Tumors; SCR = screening; SFU = safety follow-up

[a] Optional tumor marker collection in line with imaging and local standards.

[b] For subjects who discontinued treatment for any reason other than confirmed disease progression, every effort should be made to perform radiographic imaging (CT) of the chest, abdomen, pelvis, and all other known sites of disease every 3 months until documentation of confirmed disease progression per RECIST 1.1 and iRECIST, clinical progression, start of new anticancer therapy, or up to 2 years after the first dose of AMG 910, whichever occurs first.

Notes: If CT and/or MRI is done prior to ICF signature results can be used if the subjects allows its use and assessments are done within 30 days of C1 day 1, as outlined in Section 8.1.1.

There is a tolerability window of ± 1 week for the imaging assessments.

2. Introduction

2.1 Study Rationale

Combining a highly selective therapeutic target with a T cell-mediated killing mechanism has been shown to constitute an effective anticancer treatment. AMG 910 is an HLE BiTE® molecule designed to direct T cells towards **Claudin-18 isoform 2 (**CLDN18.2**)**-expressing cells. The pharmacological effect of AMG 910 is mediated by redirection of cytotoxic CD8+ or CD4+ T lymphocytes to kill CLDN18.2-expressing cells and the cytotoxic potency was demonstrated in in vitro and in vivo experiments. Based on its mechanism of action, nonclinical data, and clinical experience, both with CLDN18.2-targeting drugs and with an approved BiTE therapy, AMG 910 may address an unmet need for patients with gastric and GEJ cancer.

This is a first-in-human study in adult subjects with CLDN18.2-positive gastric adenocarcinoma or GEJ adenocarcinoma, collectively referred to as “gastric cancer” in this clinical investigation to assess the safety, tolerability, **pharmacokinetic (**PK**)**, and anti-tumor activity of AMG 910, with additional exploratory objectives to assess [redacted]

2.2 Background

2.2.1 Disease

Gastric Cancer

Gastric cancer is the **third** most common cause of cancer-related death worldwide (Torre, et al., 2015). Treatment remains challenging because the majority of patients are diagnosed at an advanced stage and limited opportunities for targeted, personalized treatment strategies exist. Most of the gastric cancers (> 90%) are adenocarcinomas, which are histologically subdivided into diffuse (undifferentiated) and intestinal (well-differentiated) types according to the Lauren classification. Approximately one third of patients present with metastatic disease at initial diagnosis and there is a shift in the site of gastric cancer towards disease of the proximal stomach and esophagogastric junction (Giacopuzzi, Bencivenga, Weindelmayer, Verlato, & de Manzoni, 2017). Patients with inoperable locally advanced and/or metastatic disease should be considered for systemic chemotherapy. Current standard of care for first line treatment is a platinum/fluoropyrimidine based doublet or triplet (c) chemo-combination therapy depending on fitness of patients. However, prognosis remains poor with median OS around 12 months (De Mello, et al., 2018). Median OS in second line treatment is

even shorter, eg, 9.6 months for patients treated with ramucirumab and paclitaxel in the RAINBOW trial (Wilke, et al., 2014).

Claudin 18.2

Claudins are a family of tight junction proteins establishing paracellular barriers which control flow of molecules between cells (Furuse, Fujita, Hiiragi, Fujimoto, & Tsukita, 1998). Depending on tissue type, different family members with their highly tissue-specific splice variants have been identified. CLDN18.2 has been found to be an epithelial surface marker for a range of malignancies including gastric, esophageal, pancreatic, lung and ovarian cancers (Sahin, et al., 2008). As expression of CLDN18.2 in normal tissue is confined to differentiated epithelial cells of the gastric mucosa, it was identified as an optimal anticancer target leading to the development and clinical evaluation of the chimeric monoclonal antibody zolbetuximab (Singh, Sudhamshi, & Huang, 2017). Completed phase 1 and 2 studies show tolerability and a phase 2b study shows clinically relevant benefit in PFS and OS to patients with CLDN18.2 positive tumors with zolbetuximab administered in first line combination with chemotherapy (Sahin, et al., 2019). The antibody is currently in phase 3 evaluation in combination with chemotherapy in patients with advanced gastric cancer (Clinical trial information: NCT01630083).

2.2.2 Amgen Investigational Product Background: AMG 910

AMG 910 is an HLE BiTE antibody construct designed to direct T cells (via CD3 binding) towards CLDN18.2-expressing cells. In AMG 910, the binding arms for CLDN18.2 and CD3 are genetically fused to the N-terminus of a single chain IgG Fc (fragment crystallizable; scFc) region. The fusion to a Fc domain is a well-established strategy to prolong the half-life of protein therapeutics, such as cytokines, growth factors, and bispecific antibodies, with several approved for the treatment of cancer (Kontermann, 2011). The extended half-life of Fc fusion proteins is due to their interaction with the neonatal Fc receptor, which results in a protected intracellular protein reservoir that is recycled to the extracellular space (Rath, et al., 2015).

A detailed description of the chemistry, pharmacology, nonclinical **PK**, and toxicology of AMG 910 is provided in the AMG 910 Investigator's Brochure **(IB)**.

2.2.2.1 Nonclinical Pharmacology

The activity of AMG 910 requires the simultaneous binding to both target cells and T cells. The pharmacological effect of AMG 910 is mediated by redirection of previously primed cytotoxic CD8+ or CD4+ T lymphocytes to kill CLDN18.2-expressing cells.

As part of the T-cell activation process, BiTE antibody constructs, such as AMG 910, cause the formation of a cytolytic synapse between T cells and target cells. The subsequent release of the pore-forming protein perforin and the apoptosis inducing proteolytic enzyme granzyme B by T cells results in the induction of apoptosis in the target cells.

AMG 910-mediated T-cell activation not only induces the directed release of cytotoxic proteins to target cells, but also results in a transient production of cytokines such as tumor necrosis factor (TNF), interferon gamma (IFN-γ), interleukin-2 (IL-2), interleukin-6 (IL-6), and interleukin-10 (IL-10).

AMG 910 monotherapy significantly prevented the development and inhibited the growth of established subcutaneous GSU luciferase (luc) tumors in mouse xenograft studies with reconstituted human T cells.

2.2.2.2 Nonclinical Pharmacokinetics

In an exploratory toxicology study in male cynomolgus monkeys, AMG 910 was administered at 30, 60, or 90 μg/kg on days 1 and 8 by IV bolus injection. The C_{max} and the AUC_{last} were dose proportional with a 20% increase in C_{max} for animals between doses on days 1 and 8.

AMG 910 toxicokinetic (TK) parameters were also assessed in a repeat-dose 1-month Good Laboratory Practice (GLP) toxicology study in the cynomolgus monkey. This study evaluated the potential toxicity and TK of AMG 910 when administered once a week by IV bolus injection over 30 days. Cynomolgus monkeys (3/sex/group) received AMG 910 at 3, 10, or 30 μg/kg. For days 1 and 22, the exposure was described by the concentration at time 0 (C_0) and the AUC_{last}. No differences (within 2-fold) in exposure, as assessed by estimating C_0 and AUC_{last}, were observed between male and female animals. AMG 910 exposure remained similar between day 1 and day 22 for anti-drug antibody (ADA) negative animals.

2.2.2.3 Toxicology

In a 1-month GLP toxicology study with a 1-month recovery period in cynomolgus monkeys, AMG 910 administered once a week at 3, 10, or 30 μg/kg by IV bolus injection was well tolerated up to 10 μg/kg with no clinical signs noted. At 30 μg/kg, 1 female was euthanized on day 15 with body weight loss and poor body condition score; cause of death was attributed to microscopic observations of marked degeneration/necrosis of the glandular epithelium in the stomach. AMG 910-related changes at all doses that were attributable to the BiTE antibody mode of action were transient and included: cytokine release; increases in white blood cells (WBC) including neutrophils; an increase in c-reactive protein (CRP) and decreases in total protein, albumin, and cholesterol indicative of an acute phase response. Minimal to mild decreases in globulin may have been indicative of gastrointestinal loss. Stomach and duodenum were identified as target organs of toxicity. AMG 910-related microscopic changes included epithelial degeneration/necrosis and subtotal mucosal loss in the stomach as well as degeneration/necrosis of Brunner's glands in the duodenum in 1 animal.

In the stomach, AMG 910-related degeneration and necrosis of glandular epithelium was minimal in males at ≥ 10 μg/kg and minimal to moderate in females at ≥ 3 μg/kg. This change is consistent with the anticipated T cell-mediated redirected lysis of target expressing cells. Degeneration and necrosis of glandular epithelium was characterized by: variable dilatation of gastric glands, often containing cellular debris; attenuation of the glandular epithelium; epithelial degeneration and necrosis; mucosal erosion and ulceration; and/or variable mixed cell inflammation with fibroplasia within the lamina propria/submucosa. Although these changes extended to the submucosal layer of the stomach, the adjacent muscular layer and serosa were unaffected, and there was no associated perforation of the gastric wall. The additional observation of glandular epithelial hypertrophy and hyperplasia in females at ≥ 10 μg/kg was considered a reparative response to the adjacent injured mucosa. No AMG 910-related macroscopic or microscopic changes were observed in animals at the end of the recovery period, indicating complete reversibility. Based on these results, the highest non-severely toxic dose (HNSTD) was considered to be 10 μg/kg.

Definitive conclusions regarding a gender effect cannot be made at this time. Groups comprised only 3 animals per sex (2 per sex for recovery groups) and therefore, it cannot be tested if there is a statistical difference between the sexes. There is no known difference in Claudin18.2 expression between female and male monkey GI tissues.

Also, no differences in exposure or in animal characteristics (weight, age) were observed. However, it cannot be ruled out that individual female human subjects may react more strongly to AMG 910 than male subjects. The study protocol provides very detailed and comprehensive instructions on the management of adverse events tailored to the individual patient situation, regardless of the subject's susceptibility to the effects of AMG 910 and/or possible gender differences (see Table 6-3 of the study protocol). A careful assessment at each visit including a detailed history, physical examination, and investigations for causes of observations also by endoscopic evaluations, should be performed and the management of adverse events and symptoms should be tailored to the individual subject's clinical situation.

2.3 Benefit/Risk Assessment

Treatment of gastric cancer remains challenging as most patients are diagnosed at an advanced stage. Thus far, immunotherapies have shown modest activity in advanced gastric cancer, and prognosis remains poor. There is a high unmet medical need for effective treatment options for patients with advanced gastric cancer.

Expression of CLDN18.2 in normal tissue is confined to differentiated epithelial cells of the gastric mucosa. The target was identified as an optimal anticancer target leading to the development and clinical evaluation of the chimeric monoclonal antibody zolbetuximab (Singh, Sudhamshi, & Huang, 2017). The antibody is currently in phase 3 evaluation in combination with chemotherapy in patients with advanced gastric cancer after observation of tolerability and clinically relevant benefit in tumors expressing CLDN18.2.

AMG 910 is a novel HLE BiTE molecule designed to direct T cells towards CLDN18.2-expressing cells. The pharmacological effect of AMG 910 is mediated by redirection of cytotoxic CD8+ or CD4+ T lymphocytes to kill CLDN18.2-expressing cells and the cytotoxic potency was demonstrated in in vitro and in vivo experiments.

Our animal data in association with human PK simulations to predict the potentially efficacious dose range clearly indicate that anticancer efficacy-related effects are expected at similar doses as assumed for on-target/off-tumor effects. In line with target expression in normal tissue, the expected on-target/off-tumor toxicity is confined to stomach mucosal toxicity. Due to the highly regenerative capacity of the stomach mucosa, recovery in the normal tissue is expected since full recovery was also observed in the GLP toxicology study at least up to the HNSTD. Careful dose escalation is therefore required to reach the predicted pharmacodynamic active dose ranges.

Moreover, detailed safety monitoring rules need to be implemented to avoid continuation of dose escalation with non-tolerable dose levels.

Based on its mechanism of action, nonclinical data, and clinical experience, both with CLDN18.2-targeting drugs and with an approved BiTE therapy, AMG 910 may address an unmet need for patients with gastric cancer. The anticipated benefit/risk profile favors the first-in-human clinical development of AMG 910 for subjects with CLDN18.2-positive gastric and GEJ cancer.

Amgen has been closely monitoring the evolving **SARS-CoV-2 Coronavirus Disease 2019 (**COVID-19**)** pandemic around the globe. As part of this effort, Amgen has performed a rigorous assessment, in discussion with study investigators, considering the study design, patient safety, public health risk, risk-benefit ratio, as well as the burden on country healthcare systems. Given the safety concerns around COVID-19 and the associated risk to maintaining normal clinical study operations, Amgen is making decisions on a study-by-study and country-by-country basis to minimize risk to patients and avoid undue burden on healthcare facilities and accordingly, is allowing enrollment to continue in studies where the potential for significant benefit in a serious or life-threatening condition exists and where site resources allow new patients to be safely enrolled and appropriately monitored.

The lack of therapeutic options available to patients with advanced gastric cancer provides a strong rationale for treatment in a clinical study with AMG 910. Potential risks associated with study participation, in particular with added challenges due to COVID-19, may be outweighed by anticipated benefits associated with the study treatment.

There are no Amgen data to inform the incidence or severity of COVID-19 infections in patients receiving AMG 910. Patients who display symptoms consistent with COVID-19 infections or who have tested positive for COVID-19 should urgently contact their site medical monitor to ensure appropriate care as well as documentation and management of study activities, which may include but are not limited to temporarily withholding investigational product.

Amgen considers that it is important to continue the proposed development of AMG 910 in this study in order to advance potential therapy options for patients as rapidly as possible, while balancing this with appropriate measures to monitor and mitigate the potential impact of COVID-19.

Reference should be made to the Investigator's Brochure for further data on AMG 910.

2.3.1 Therapeutic Context

Although a modest success was noted with the anti-**human epidermal growth factor receptor 2 (**HER2**)** targeting antibody trastuzumab, the median OS of 13.8 months reported for the combination of trastuzumab with standard chemotherapy in the Trastuzumab for Gastric Cancer (ToGA) trial represents only an incremental increase over standard of care and treatment is associated with an increased risk for a drop in left ventricular ejection function
(Bang, et al., 2010; Chen, et al., 2011). Newer HER-2 targeting approaches (trastuzumab-DM1, T-DM1 or lapatinib) have not been able to show improvements in OS, either in the naïve or in the pre-treated patient population (Lopez, Harada, Mizrak Kaya, & Ajani, 2018).

With immune checkpoint inhibition coming of age, another modest improvement in prognosis for patients with advanced gastric cancer was seen. Evaluation of the PD-1 targeting antibody nivolumab, revealed an improvement in OS from 4.1 months in the standard of care group to 5.3 months, observed with nivolumab in patients with unresectable advanced or recurrent disease and failure after 2 or more previous chemotherapies (Kang, et al., 2017). Results, however, were not interpreted in correlation with **programmed death-ligand 1 (**PD-L1**)** expression status.

In the KEYNOTE-059 trial, impressive **objective response (**OR**)** results were reported for patients receiving monotherapy with pembrolizumab after failure of 2 or more previous chemotherapy lines if tumors were positive for PD-L1 expression and belonged to the subset of microsatellite instability-high (MSI-H) tumors (Bang, et al., 2017). However, although some of the observed responses were durable, in total it is only a small subfraction of the patients responding to the treatment. The OR rate was 11.6% for all patients and 15.5% for patients with PD-L1 positive tumors (Fuchs, et al., 2018). In KEYNOTE-061, a study comparing front-line pembrolizumab monotherapy versus combination of pembrolizumab with chemotherapy versus chemotherapy alone in patients with unresectable locally advanced or metastatic gastric cancer, an OR rate of 57.1% was observed with pembrolizumab monotherapy and OR rate of 64.7% was observed for the combination of pembrolizumab with chemotherapy in the MSI-H subpopulations (Shitara, Van Cutsem, & Bang, 2019).

In light of numerous failures of studies evaluating targeted treatment strategies in advanced upper gastrointestinal malignancies directed against VEGFR, mesenchymal epidermal transition (c-MT) or epidermal growth factor receptor (EGFR), the search for and evaluation of new targets and therapeutic approaches is of utmost interest.

The combination of a highly selective therapeutic target with a T cell-mediated killing mechanism has been shown to constitute an effective anticancer treatment.

Clinical experience with other BiTE antibody molecules in other tumor indications provides a therapeutic context for clinical exploration of AMG 910 (Hummel, et al., 2019; Klinger, Benjamin, Kischel, Stienen, & Zugmaier, 2016).

2.3.2 Key Benefits

This study is the first-in-human trial of AMG 910. Key benefits in humans will be investigated and will be described when data become available. Potential benefits may include reduction or regression of gastric cancer disease burden and improvement of symptoms as seen with other CLDN18.2-targeting agents (Sahin, et al., 2018; Sahin, et al., 2019).

2.3.3 Key Risks

Available clinical data are summarized in the most recent version of the IB. The key safety risks for AMG 910, summarized in Table 2-1 below, are based on the biological mechanism of action and the potential for off-tumor effects in the gastrointestinal tract.

Table 2-1. Key Risks for AMG 910

Safety Risk	Description
Cytokine Release Syndrome (CRS) / Infusion-Related Reactions	CRS is a systemic inflammatory response characterized by a release of cellular cytokines. Clinical signs and symptoms of CRS may 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 Infusion reactions may be clinically indistinguishable from manifestations of CRS.
Gastrointestinal Toxicity	Stomach and duodenum were identified as target organs of toxicity in the cynomolgus monkey. Potential gastrointestinal associated adverse events may include: • Constitutional – decreased appetite, decreased food intake, weight decreased, anorexia, malnutrition, fatigue, and asthenia. • Gastrointestinal – nausea, vomiting, gastritis, enteritis, abdominal pain, diarrhea, constipation, hematemesis, blood in stool, gastrointestinal ulcer, gastrointestinal hemorrhage, gastrointestinal perforation, and gastrointestinal fistula.

Other safety considerations for this study are described below.

- Neurologic Events: A wide range of commonly observed neurological symptoms has been associated with the use of another BiTE molecule, blinatumomab (anti-CD19 BiTE antibody construct) in patients with acute lymphoblastic leukemia (ALL). However, the full spectrum of neurologic events has not been observed in clinical trials for other BiTE molecules, and the neurotoxicity may in part be associated with targeting CD19. No neurologic events were observed in the AMG 910 1-month GLP toxicology study in cynomolgus monkeys. Although AMG 910 binds CLDN18.2 and is a different construct from CD19 T cell engagers, the potential for neurologic events will be monitored as a precautionary measure in these patients.
- Tumor Lysis Syndrome (TLS): While rare in gastric cancer, TLS is a severe, life-threatening disorder that can occur in highly proliferative malignancies or with debulking of extensive tumor burden. Signs and symptoms may include hyperkalemia, hyperphosphatemia, hyperuricemia, hyperuricosuria, and hypocalcemia, potentially causing lethal cardiac arrhythmias, seizures, and/or renal failure. There is possible occurrence of TLS in patients with high tumor load, hence TLS will be monitored in these patients.
- Sucrose Toxicity: The drug product AMG 910 contains sucrose. Renal toxicity following IV administration of sucrose can occur secondary to high solute load resulting in osmotic damage (Haskin, Warner, & Blank, 1999). Cases of renal dysfunction have been reported with IV administration of some marketed products containing sucrose (Orbach, Tishler, & Shoenfeld, 2004).

Refer to the AMG 910 Investigator's Brochure for further description of key safety risks.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of AMG 910 in adult subjects • To determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D)	• Dose-limiting toxicities (DLT) • Treatment-emergent adverse events • Treatment-related adverse events • Changes in vital signs, electrocardiogram (ECG), and clinical laboratory tests

Objectives	Endpoints
Secondary	
• To characterize the PK of AMG 910	• PK parameters for AMG 910 following **short-term** intravenous (IV) **and extended IV (eIV)** administration including but not limited to maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), area under the concentration-time curve (AUC) over the dosing interval, accumulation following multiple dosing, and, if feasible, half-life ($t_{1/2}$)
• To evaluate preliminary anti-tumor activity of AMG 910	• Objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and iRECIST • Duration of response (DOR) • Time to progression • Progression-free survival (PFS), 6-month and 1-year PFS • Overall survival (OS), 1 and 2-year OS

Exploratory	
[redacted]	

[redacted]

4. Study Design

4.1 Overall Design

This is an open-label, ascending, multiple dose, phase 1 study evaluating AMG 910 in subjects with CLDN18.2-positive gastric adenocarcinoma. The study will consist of:

- Dose-exploration phase
- Dose-expansion phase

The dose-exploration phase of the study will estimate the MTD of AMG 910 using a **Bayesian logistic regression model (**BLRM**)**. A RP2D may be identified based on emerging safety, efficacy, and pharmacodynamic data prior to reaching an MTD. Following the dose-exploration phase, a dose-expansion phase will be conducted to confirm safety, PK, and pharmacodynamics at the MTD or RP2D and to obtain further safety and efficacy data and enable correlative biomarker analysis.

Because of the observation of cytokine release syndrome (CRS) events in cohort 1, the dosing of AMG 910 and the dose escalation schedule will be adapted and AMG 910 will be administered in cycle 1 week 1 as an extended intravenous (IV) infusion (eIV) for 96 hours starting on day 1 followed by weekly short-term IV infusions (approximately 60 minutes) for all cycles of subjects enrolled in next cohorts (cohorts 1b and beyond).

Furthermore, the following modifications may be recommended by the Dose Level Review Team (DLRT) depending on the observed safety and efficacy observed in all prior cohorts:

- **To adapt duration of eIV administration during cycle 1 week 1 within a range of 3 to 7 days**
- **To switch to the twice weekly dosing schedule after cycle 1 week 1 and administer AMG 910 as follows:**
  - For cycles 1 and 2, twice a week at days 1 and 3 of each week in a 28-day cycle**, starting with cycle 1 day 8 dose** and
  - For cycles 3 to 6, weekly, ie, days 1, 8, 15, and 22 in a 28-day cycle

There will be treatment-free intervals of 2 weeks after cycles 2 and 4.

The treatment-free intervals may be extended up to 3 weeks to allow for recovery in case of adverse events. The treatment-free interval after cycle 4 may also be extended to 3 weeks for logistical reasons.

The maximum treatment duration will be 6 cycles. Subjects who have shown no disease progression and no worsening of performance status at the end of cycle 6 may continue treatment for an additional 2 cycles if there are no unresolved grade 3 or 4 toxicities and if the investigator and the Amgen Medical Monitor agree that continued treatment may likely provide benefit for the subject. Further extensions of the treatment are to be agreed upon in the same manner at the end of each second cycle of extended treatment.

Subjects who have derived sustained benefit from treatment, meaning at least stable disease and no worsening of performance status, for at least 3 months after the end of treatment but experience relapse or progression thereafter, and have not received any other systemic anti-cancer therapy since their last AMG 910 treatment, may be retreated in a separate retreatment group. Treatment will be administered at the highest dose level assessed as safe at the time of retreatment initiation.

The DLRT may explore 2 different AMG 910 dosing schedules in cohorts running in parallel.

The safety, tolerability**,** and preliminary anti-tumor activity of AMG 910 in combination with other therapeutic agents may potentially be explored and subject to future protocol amendment(s). After review of emerging data on the safety, tolerability, PK and preliminary anti-tumor activity of AMG 910, the protocol may be amended to include additional cohorts. The rationale for amending and the data supporting the rationale will be included in the amended protocol(s).

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

4.2 Number of Subjects

Approximately 70 subjects will be enrolled in the study, with approximately 34 subjects in the dose escalation cohort and 36 subjects in the dose expansion cohort.

Patients in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 9.2.

4.2.1 Replacement of Subjects

Subjects who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose escalation decisions and MTD determination and will be replaced by an additional subject at that same dose level, as necessary, to ensure that all dose escalation decisions are made with sufficient safety data (eg, safety data from at least 3 evaluable subjects in a multi-subject cohort).

4.2.2 Number of Sites

Approximately 30 investigative sites in North America, Europe, and Asia will be included in the study. Sites that do not enroll subjects within 4 months of site initiation may be closed.

4.3 Justification for Investigational Product Dose

The PK of AMG 910 in humans was estimated using allometric scaling of PK parameters obtained from nonclinical studies in cynomolgus monkeys at doses ranging between 3 to 30 μg/kg.

[redacted]

[redacted]

As recommended by the ICH S9 guidance (ICH S9) the selection of the starting dose for this first-in-human study was based on the Minimum Anticipated Biological Effect Level (MABEL). Consistent with the acceptable approaches for FIH dose selection of CD3 bispecific constructs highlighted by Saber et al. (Saber, Del Valle, Ricks, & Leighton, 2017), the starting dose is based on the half maximal effective AMG 910 concentration (EC_{50}) of the most sensitive in vitro parameter of AMG 910 activity in the most sensitive cells, which was T cell redirected cell lysis on co-cultured of gastric carcinoma GSU tumor cells.

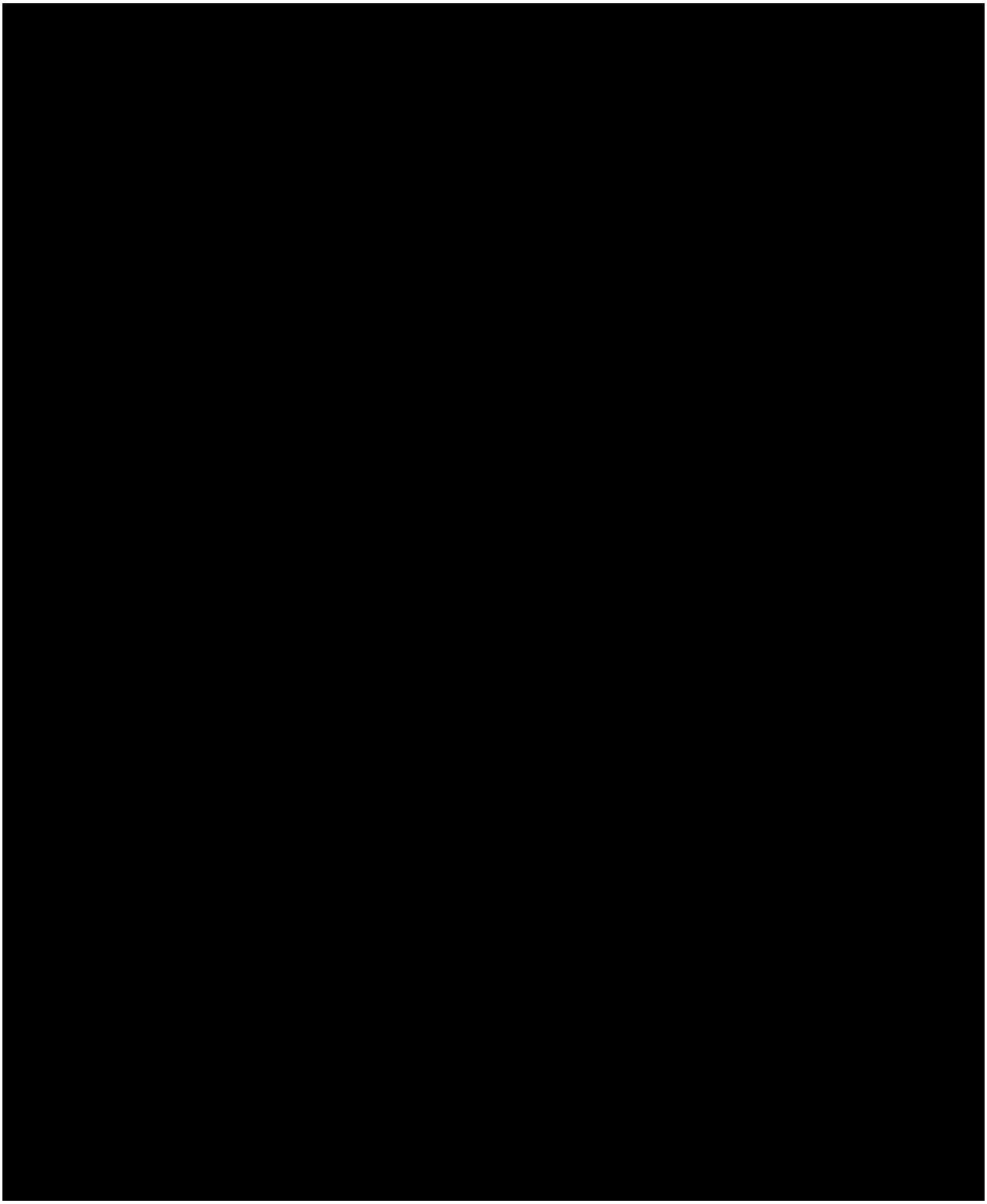
A starting dose of 6.5 μg was selected based on human PK prediction and is predicted to generate first dose maximum serum concentrations (C_{max}) **to** approximate the MABEL. [redacted]

[redacted]

[redacted]

The starting dose and dosing regimen are also supported by the GLP toxicology study in cynomolgus monkeys. The HNSTD in cynomolgus monkeys was determined to be

10μg/kg. The predicted human steady state exposure after a starting dose of 6.5 μg is approximately 19-fold and 59-fold lower for area under the concentration-time curve (AUC) and C_{max}, respectively, compared to the exposure in cynomolgus monkeys at the HNSTD.



4.4 End of Study

An individual subject is considered to have completed the study if he/she has completed the last visit or the last scheduled procedure shown in the Schedule of Activities **(SoA)**. The total study duration for an individual subject is up to 2 years.

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

4.5 Patient Input on Study Design

There was no patient input on study design.

5. Study Population

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

Eligibility criteria will be evaluated during screening.

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

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

5.1 Inclusion Criteria

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

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures (see Section 8.1).

102 Age ≥ 18 years **(or ≥ legal adult age within the country if it is older than 18 years)** at time of signing the informed consent**.**

103 Subjects with histologically or cytologically confirmed metastatic or locally advanced unresectable gastric adenocarcinoma or GEJ adenocarcinoma positive for CLDN18.2 as defined by the test described herein (Section 8.2.10.1). Prior treatment with any CLDN18.2-targeting product requires testing of a tissue sample obtained after the treatment with the CLDN18.2-targeting product (not applicable for re-treatment).

104 Subjects should not be eligible for curative surgery and should have been refractory to or have relapsed after 2 or more prior lines of standard systemic therapy that included a platinum, a fluoropyrimidine, either a taxane or irinotecan, and an approved VEGFR antibody/TKI **and depending on country-specific standards and approvals**.

105 For subjects eligible for HER2 directed therapy, prior therapy should have included an approved HER2 targeting antibody.

106 Subjects may also be included if the aforementioned therapeutic options were medically not appropriate for them. In these cases, the reason(s) why required prior therapies for gastric cancer were medically not appropriate should be documented in the subject's eCRF.

107 For dose expansion only: Subjects with at least 1 measurable lesion ≥ 10mm which has not undergone biopsy within 3 months of screening scan. This lesion cannot be biopsied at any time during the study.

108 Subject agrees to gastroscopic evaluations during screening and at least once during the treatment period, and is an appropriate candidate for a tumor biopsy, if applicable.

109 Subject has ECOG performance status 0 to 1.

110 Life expectancy ≥ 3 months, in the opinion of the investigator.

111 Adequate organ function, defined as follows:

- hematological function:

  absolute neutrophil count ≥ 1 x 10^9/L (without growth factor support within 7 days from screening assessment)

  platelet count ≥ 75 x 10^9/L (without platelet transfusion within 7 days from screening assessment)

  hemoglobin > 9 g/dL (90 g/L) (without blood transfusion within 7 days from screening assessment)

- renal function:

  calculated or measured creatinine clearance ≥ 50 mL/min using:

  the MDRD formula (Levey, et al., 2006) OR

  via 24-hour urine collection with plasma and urine creatinine concentrations

- hepatic function:

  aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x ULN (or < 5 x ULN for subjects with liver involvement)

total bilirubin (TBL) < 1.5 x ULN (or < 2 x ULN for subjects with liver metastases)

albumin ≥ 2.5 g/dL (25 g/L)

- coagulation function:

  Prothrombin time **(PT) or** international normalized ratio **(**INR) and partial thromboplastin time **(PTT) or activated partial thromboplastin time** (**a**PTT) ≤ 1.5 x ULN (for subjects receiving anticoagulation therapy < 2.0 x ULN)

112. Subjects with stable condition and anti-coagulative therapy ongoing for at least 1 month, no obvious signs and symptoms of bleeding, and coagulation parameters as defined in inclusion criteria 111 are fulfilled.

113. Subjects should be able to use proton pump inhibitors.

5.2 Exclusion Criteria

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

Disease Related

201 Any anticancer therapy or immunotherapy within 4 weeks of start of first dose (14 **days** for palliative radiation).

202 Untreated or symptomatic central nervous system (CNS) metastases, leptomeningeal disease, or spinal cord compression.

Other Medical Conditions

203 Prior major surgery within 4 weeks of first dose.

NOTE: Biopsy or long line insertion are not considered a major surgery.

204 Presence of fungal, bacterial, viral, or other infection requiring IV antimicrobials or antivirals for management within 7 days of dosing

NOTE: Simple urinary tract infections and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with sponsor. Screening for chronic infectious conditions is not required.

205 Positive test for Human Immunodeficiency Virus (HIV).

206 Exclusion of hepatitis infection based on the following results and/or criteria:

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

- Negative HBsAg and positive for hepatitis B core antibody: Hepatitis B virus **(HBV)** DNA by polymerase chain reaction (PCR) is necessary. Detectable **HBV** DNA suggests occult hepatitis B **(subjects with positive hepatitis B core antibody and/or hepatitis B surface antibody accompanied by a negative HBV-DNA can be enrolled into the study, but HBV-DNA needs to be monitored every 2 months)**.
- Positive Hepatitis C virus antibody (HCVAb): Hepatitis C virus RNA by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C.

207 History of arterial thrombosis (eg, myocardial infarction, stroke**,** or transient ischemic attack) within 12 months of first dose of AMG 910

208 History or presence of clinically relevant CNS pathology such as uncontrolled epilepsy or seizure disorder, non-traumatic paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, and psychosis

209 Unresolved toxicities from prior anti-tumor therapy not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade 1, with the exception of alopecia and grade 2 peripheral neuropathy, which has been unchanged within the last 2 months AND there is agreement to allow by both the investigator and sponsor

210 History of other malignancy within the past 2 years, with the following exception(s):

- Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before enrollment and felt to be at low risk for recurrence by the treating physician.
- Adequately treated non-melanoma skin cancer or lentigo malignant without evidence of disease.
- Adequately treated cervical carcinoma in situ without evidence of disease.
- Adequately treated breast ductal carcinoma in situ without evidence of disease.
- Prostatic intraepithelial neoplasia without evidence of prostate cancer.
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ.

211 Autoimmune disorders requiring chronic systemic steroid therapy or any other form of immunosuppressive therapy while on study, eg, ulcerative colitis or Crohn's disease, or any other gastrointestinal autoimmune disorder causing chronic nausea, vomiting, or diarrhea. Recent or current use of inhaled steroids or physiological substitution in case of adrenal insufficiency is not exclusionary.

212 Evidence or history within last 3 months of gastrointestinal inflammatory conditions not associated with the underlying cancer disease including gastrinomas, duodenitis, proven gastric ulcer, duodenal ulcer, pancreatitis, or subject with recent gastric bleeding. Subjects may be included if the symptomatic/immunosuppressive treatment is discontinued more than 4 weeks prior to the first dose of AMG 910, symptoms have resolved, and gastroscopy does not indicate signs of active disease.

213 Subjects in need of long-term antiplatelet treatment (aspirin, dosage > 300 mg/d; clopidogrel, dosage > 75 mg/d).

214 Subject has gastric outlet syndrome or persistent recurrent vomiting.

225 Subjects with inherited bleeding disorders (eg, Willebrand's disease, hemophilia A and other clotting factor deficiency) and subjects with known heparin-induced thrombocytopenia.

226 Subjects requiring non-steroidal anti-inflammatory drugs (NSAIDs) during study treatment. The NSAID(s) should be stopped within 7 days prior to start of treatment.

Prior/Concurrent Clinical Study Experience

215 Currently receiving treatment in another investigational device or drug study, or less than 4 weeks since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Other Exclusions

216 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 75 days after the last dose of AMG 910.

217 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 75 days after the last dose of AMG 910. Refer to Section 11.5 for additional contraceptive information.

219 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 5 months after the last dose of AMG 910. Refer to Section 11.5 for additional contraceptive information.

220 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional 5 months after the last dose of AMG 910.

221 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 5 months after the last dose of AMG 910.

222 Subject has known sensitivity to any of the components of AMG 910 to be administered during dosing.

223 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.

224 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

5.3 Subject Enrollment

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

Due to multiple sites participating in the dose escalation part, a close communication is necessary between Amgen and local study teams to allow parallel screening of subjects. The Amgen representative communicates when treatment slots become available. When a site identifies a potential subject, the local study team sends an email to Amgen with the planned consent date, planned screening date, planned treatment date, and a statement with respect to urgency of treatment need for this potential subject. The Amgen representative will confirm slot reservation for screening back to the local study team. Subjects may be eligible to enroll once all screening tests and procedures are completed and results indicate that all eligibility criteria are met. The local study team will complete and send the enrollment eligibility documentation to the sponsor or designee. The Amgen representative will acknowledge receipt and send confirmation of cohort and dose level assignment for the subject. The start of patient dosing will be staggered by at least 72 hours as described in Section 6.2.1.1.2.

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

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

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

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

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, 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 once. Refer to Section 8.1.1.

6. Treatments

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

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

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

6.1 Treatment(s) Administered

6.1.1 Investigational Products

Table 6-1. Study Treatments

Study Treatment Name	**Amgen Investigational Product[a]: AMG 910**
Dosage Formulation	AMG 910 is supplied as a sterile, preservative-free lyophilized powder for IV administration after reconstitution with sterile water for injection (WFI). After reconstitution with 1.2 mL of sterile WFI, the 1.0 mg/mL AMG 910 drug product is formulated with L-glutamic acid, sucrose, and polysorbate 80, pH 4.2. The final container is a single-use, 6cc glass vial and contains deliverable dose of 1 mg AMG 910.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	This is a dose-exploration/dose-expansion study (dose range: 6.5 **to 2000** µg). See Sections 6.2.1.1 and 6.2.1.2 for further details regarding dose exploration and expansion. AMG 910 will be administered **once or** twice a week in a 28-day cycle. There will be treatment-free intervals of 2 weeks after cycles 2 and 4. **For details of the dosing schedule, see Section 4.1.**
Route of Administration	**eIV infusion for 4 days starting on cycle 1 day 1 (may be modified to 3 to 7 days per DLRT recommendation)** Short-term IV infusion (approximately 60 minutes)
Accountability	The planned dose, dose received, start date/time, stop date/time, and lot number of investigational product are to be recorded on each subject's CRF(s).
Dosing Instructions	AMG 910 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 910 may be administered through a peripheral venous line or a central venous access if available. To ensure delivery of the total dose, a sufficient flush volume will be infused at a controlled rate after the dose has been administered. The drug should not be administered as a bolus. **For eIV infusion, a reliable venous access like a central venous line, a venous access port, or equivalent is required to ensure continuous administration over 96 hours (eg, port-a-cath or PICC line).** **The dosing schedule for an individual subject will not change throughout the treatment period.** See IPIM for more detailed information regarding the storage, preparation, destruction, and administration of AMG 910.

Page 1 of 2

Footnotes defined on next page of the table

Table 6-1. Study Treatments

Study Treatment Name	Amgen Investigational Product[a]: AMG 910
Hospitalization Guidance	All subjects will be hospitalized for intensive monitoring for the times given below. The subjects may be discharged after these hospitalization periods if there are no grade ≥ 2 adverse events at least possibly related to AMG 910. Minimum hospitalization times for subjects will be as follows: • cycle 1: – **during eIV infusion for a minimum of 4 days** – 48 hours after dosing on day 8 – 24 hours after dosing on days **15** and **22 with weekly dosing (on days 10, 17, and 24 in cohorts with twice weekly dosing)** • cycle 3: – 24 hours after dosing on day 1 • for cycles 1 and 3: study sites must have immediate access to a medical intensive care unit staffed by critical care providers • cycles 2, 3, 4, 5, and 6: subject should be monitored intensely in hospital or outpatient clinic for at least 4 hours after end of each infusion (except cycle 3 after dosing on day 1, see above) and for 8 hours after end of infusion on cycle 3 day 8 • cycles 2, 4, 5 and 6: hospitalization not required unless a subject experiences an adverse event requiring hospitalization as described in Table 6-3, or if clinically indicated • re-start of treatment after an interruption due to adverse event: Refer to Table 6-3 in case of retreatment the same hospitalization guidance applies as for initial treatment at the dose level and schedule to be administered.

Page 2 of 2

DLRT = Dose Level Review Team; eIV = extended intravenous; IV = intravenous**; PICC = peripherally inserted central catheter.**

[a] AMG 910 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Non-investigational Products

In some regions, such as the European Union, the protocol-required therapies described in Section 6.1.4 are administered to prevent/reduce the severity of infusion-related reactions or CRS, or to treat CRS (eg, IV glucocorticoids and tocilizumab) or proton pump inhibitors (PPIs) for prophylactic/concomitant treatment of gastric symptoms, are considered to be rescue medications, a category of non-investigational medicinal products.

6.1.3 Medical Devices

A diagnostic test will be used to select subjects for treatment based on subject samples collected retrospectively or prospectively during the study. The diagnostic test is intended to measure CLDN18.2 in tumor tissue, as further described in Section 8.2.10.

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

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

6.1.4 Other Protocol-required Therapies

All other protocol-required therapies including glucocorticoids, proton pump inhibitors 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.

Prophylactic/concomitant treatment with a proton pump inhibitor starting approximately 1 hour prior to start of AMG 910 infusion is recommended. [redacted]

All sites will ensure that CRS rescue medications are available on-site, including corticosteroids and 2 doses of tocilizumab per study subject.

After observation of a grade ≥ 2 CRS in the study, mandatory premedication with dexamethasone will be introduced according to the following instructions:

- Dexamethasone 8 mg orally (or equivalent dose of other corticosteroids) to be administered 6 to 16 hours prior to all doses of AMG 910 during the first 2 weeks of dosing.
- Additionally, dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) to be administered within 1 hour prior to all doses of AMG 910 during the first 2 weeks of dosing.

- After 2 weeks of premedication, dexamethasone administration can be at the discretion of the investigator.
- The same pretreatment regimen should be administered for 1 week of dosing after any treatment interruption longer than 5 days.
- For subsequent cycles, dexamethasone may be administered prior to AMG 910 per investigator discretion after consultation with the Amgen medical monitor.

The DLRT may modify premedication dosing regimen based on emerging safety data.

6.1.5 Other Treatment Procedures

There are no other treatment procedures in this study.

6.1.6 Product Complaints

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

This includes any investigational product(s) provisioned and/or repackaged/modified by Amgen (ie, AMG 910).

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

6.1.7 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 safety follow-up):

- Any antitumor therapy other than AMG 910, 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
- Exception: recommended preventive vaccinations may be administered in the treatment-free intervals (such as anti-flu or other anti-infective vaccinations)**; however, such vaccinations should not be given during the DLT period of an individual subject.**

- Chronic systemic corticosteroid therapy or 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). Recent or current use of inhaled steroids or physiological substitution in case of adrenal insufficiency is not exclusionary.
- Long-term antiplatelet treatment (aspirin, dosage > 300 mg/d; clopidogrel, dosage > 75 mg/d)
- Any other investigational agent
- Any major surgery

6.2 Dose Modification

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

6.2.1.1 Dose-exploration Phase

The dose-exploration phase of the study will enroll up to 34 subjects with gastric cancer. Table 6-2 describes the planned dose levels for investigation. Dose exploration will be conducted in 2 stages: single-subject cohort(s) followed by multiple-subject cohort(s) (3 to 4 subjects per cohort).

Table 6-2. Planned AMG 910 Target Doses per Dose Cohort Level

Cohort number	Number of subjects[a]	Dose (μg) **Route**
(-1)	**(3 to 4)**	**2.5 IV**
1	**3 to 4**	6.5[b] **IV**
1b	**3 to 4**	**6.5[b] eIV**
2**b**	**3 to 4**	**15 eIV**
3**b**	3 to 4	**30 eIV**
4**b**	3 to 4	**60 eIV**
5**b**	3 to 4	**150 eIV**
6**b**	3 to 4	**300 eIV**
7**b**	3 to 4	**600 eIV**
8**b**	3 to 4	1000 **eIV**
9**b**	3 to 4	**2000 eIV**

Routes of administration: eIV = extended intravenous; IV = **short-term** intravenous**.**
[a] Switching from a single subject cohort to a multiple-subject cohort will occur with cohort 3 or sooner if specific safety criteria are observed as described in Section 6.2.1.1.1.
[b] If a dose reduction is needed according to instructions provided in Table 6-3, treatment will be continued at a dose of 2.5 μg as specified in Section 6.2.2.3.5.
Note: The "b" cohort numbers are used to differentiate cohorts 1 through 10 denoted in previous versions of the protocol.

6.2.1.1.1 Single-subject Cohorts

The starting dose will be based on the MABEL (Saber, Del Valle, Ricks, & Leighton, 2017). Dose exploration will begin with single-subject cohort(s). The starting dose is expected to have the first dose C_{max} below the MABEL. Serum concentrations to be achieved with first 3 to 4 dose level cohorts are expected to be lower than those at which pharmacodynamic activity translating into treatment-related adverse events or efficacy is predicted to be observed. Therefore, the first 2 cohorts are pre-planned single subject cohorts.

If a subject in the first single-subject cohort does not experience a grade 2 or higher adverse event at least possibly related to AMG 910 or DLT (Section 6.2.1.3) during the initial 28 days of treatment (DLT window for single-subject cohorts), then the next subject may be dosed at the next higher dose level(s) per Table 6-2.

In consequence, switching from a single subject cohort to a multiple-subject cohort will occur with cohort 3 or sooner if any of the following safety criteria are observed during the DLT window:

- DLT (Section 6.2.1.3), or
- Grade $\geq$ 2 adverse events based on CTCAE version 5.0, at least possibly related to AMG 910, with the exception of lymphopenia or lymphocyte count decreased.

NOTE: See Table 6-3 for CRS and TLS grading criteria.

The DLRT will convene to review the safety data and recommend the appropriate dose to be implemented. The recommended dose will not exceed the levels recommended by the BLRM in the dose escalation portion and the next pre-defined dose level listed in Table 6-2. The DLRT may also convene ad hoc meetings any time to review safety data if deemed necessary.

Determination of whether a subject is evaluable for DLT assessment will be made by DLRT in accordance with the following rules:

- Subjects who receive study treatment (at least 80% of the planned dose for cycle 1) and remain on study through the DLT assessment window will be considered DLT-evaluable.
- Subjects who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD determination and may be replaced by an additional subject at that same dose level.

6.2.1.1.2 Multiple-subject Cohorts

Dose escalation in multiple-subject cohorts (3 **to** 4 subjects per cohort) will begin as described in Section 6.2.1.1.1 and follow the planned schedule shown in Table 6-2. Sequential dosing of subjects by at least 72 hours should be employed to all subjects within a dose escalation cohort. The DLRT will convene to review the safety data and recommend the appropriate dose to be implemented. The recommended dose will not exceed the levels recommended by the BLRM in the dose escalation portion and the next dose level listed in Table 6-2. The DLRT may recommend enrolling more subjects for safety reasons at any point during the study.

For dose escalation with eIV dosing schedule, the DLRT will in addition to the considerations above evaluate the eIV administration and the short-term IV administrations separately for the occurrence of first-dose effects (eg, CRS and TLS). The DLRT will review the safety data and may recommend to only escalate the dose for either the eIV administration or the short-term infusion administrations for the next cohort. The recommended dose will not exceed the levels recommended by the BLRM in the dose escalation portion and the next dose level listed in Table 6-2. For subsequent dose escalation decisions, the dose for the eIV administration and the short-term IV administrations may be again escalated in parallel while maintaining the relative dose difference or the dose for the not escalated administration may be kept constant.

For multiple-subject cohorts, the DLRT will not recommend dose escalation decisions until each of the following occurs:

- All subjects in the cohort have been followed for safety events for a minimum of 28 days from the first dose of AMG 910 (except if a subject experienced a DLT) or have been followed for a minimum of 72 hours after the seventh dose with treatment interruption not constituting a DLT, whatever is longer.
- At least 3 of the subjects can be evaluated for DLT assessment

Determination of whether a subject is evaluable for DLT assessment will be made by DLRM in accordance with the following rules:

- Subjects who receive study treatment (at least 80% of the planned dose for cycle 1) and remain on study through the DLT assessment window will be considered DLT-evaluable.
- Subjects who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD determination and may be replaced by an additional subject at that same dose level.

Dose Level Determination

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

Dose Cohort Stopping Rules

Dose escalation will follow the pre-defined dose levels in Table 6-2 until a subject experiences a DLT. Then the dose for the subsequent cohorts will be decided by the DLRT after evaluating all available safety, laboratory, and PK data as well as the recommendation from the BLRM. Dose escalation/de-escalation decisions in multiple-subject cohorts will be guided by the BLRM model of dose toxicity. The MTD for BLRM is the dose level predicted to have the highest probability of a DLT rate within the target interval of 20% to 33%, subject to overdose control. To control the risk of overdose, the MTD must have less than a 40% predicted probability of overdosing (DLT rate $>$ 33%).

If late onset adverse events (ie, after the 28-day DLT period) occur or late findings from endoscopic evaluations are reported during a cohort, the DLRT may adaptively re-consider the doses evaluated within a cohort for subsequent dosing and/or possibly trigger a de-escalation or withholding of additional doses in subsequent cohorts. Based on the BLRM model and after reviewing all available safety and tolerability data, the DLRT may recommend dosing at intermediate dose levels between the planned dose levels in Table 6-2.

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

Dose escalations will end once any of the following events occur:

- Highest planned dose level is determined to be safe and tolerable (minimum of 6 treated subjects on this dose level).
- The MTD is identified. A dose level is considered the MTD when the BLRM recommends treatment at this dose level and 6 or more evaluable subjects have already been treated at this dose level.

- On the basis of a review of real-time safety data and available preliminary PK data, dose escalation may be halted or modified by the Sponsor as deemed appropriate. A re-evaluation of the risk/benefit for the study will be necessary after the following observations:
- Gastrointestinal events of CTCAE grade 3 in 2 subjects, with the exemption of nausea, vomiting, and abdominal pain, and gastrointestinal events of CTCAE grade 4 in 2 subjects if events are at least possibly related to AMG 910
- Gastrointestinal event of CTCAE grade 5 in 1 subject, at least possibly related to AMG 910

To acquire additional safety and pharmacodynamic data to better inform the RP2D, additional subjects may be enrolled at a dose level that has been shown to not exceed the MTD based on the dose-escalation criteria described above, and at which there is evidence of anti-tumor activity and/or pharmacodynamic biomarker modulation. Up to approximately 3 additional subjects per dose level may be enrolled.

6.2.1.2 Dose-expansion Phase

Upon completion of the dose exploration part of the study, up to approximately 36 additional subjects will be enrolled in the dose expansion part to gain further clinical experience, safety and efficacy data for AMG 910 in subjects with gastric adenocarcinomas. The dose to be evaluated will be at or below the MTD estimated in the dose exploration cohorts. A final estimate of the MTD and RP2D will be evaluated and confirmed utilizing all DLT-evaluable subjects from the dose exploration and the dose expansion cohorts. This final estimate of the MTD and RP2D will not exceed the MTD identified in the dose escalation portion of the study and will not exceed the MTD identified in the dose escalation portion of the study by the BLRM. Efficacy data will be reviewed in the dose expansion part of the study after the first 15 subjects are enrolled and have had the opportunity to receive at least 8 weeks of treatment and received the first response assessment (with recruitment ongoing). Dose expansion may be discontinued early; the guidelines for early stopping due to insufficient efficacy and the guidelines for early stopping due to excessive toxicity are detailed in Section 9.4.1.1. The DLRT may also convene ad hoc meetings any time to review safety data if deemed necessary. A final BLRM estimate of the MTD will use all data from dose exploration and dose expansion.

6.2.1.3 Dose-limiting Toxicity

The adverse event grading scale to be used for this study will be the CTCAE version 5.0 and is described in Section 11.4, with the exception of CRS, which will be graded using

the criteria referenced in the publication by Lee et al (2014) (see Section 11.13) and TLS, which will be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al (2008) (see Section 11.14).

Dose-limiting toxicities are defined as any adverse events at least possibly related to AMG 910 with an onset within the first 28 days following first dose for single-subject cohorts and within the safety observation period for multiple-subject cohorts as defined in Section 6.2.1.1.2 with any of the following criteria:

- grade 2 gastric perforation or fistula
- grade ≥ 3 non-hematologic adverse events including laboratory abnormalities with the exceptions as stated below:
    - grade 3 fever (not associated with any other CRS/**infusion-related reaction** symptoms) that does improve to grade ≤ 1 within 72 hours
    - grade 3 nausea, vomiting, or diarrhea that does improve to grade ≤ 1 or baseline within 72 hours with optimal medical support.
    - grade 3 asymptomatic liver enzyme elevations including AST, ALT, GGT with AST improving to grade ≤ 2 within 72 hours and ALT and GGT, which have long half-lives, improving to grade ≤ 2 within 7 days except those meeting Hy's Law
- re-challenge with AMG 910 after treatment interruption due to any stomach toxicity results in at least same stomach toxicity and is of CTCAE grade ≥ 3 or grade 2 and ongoing for more than 3 days despite optimal supportive treatment
- grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding
- grade 4 neutropenia lasting longer than 28 days
- febrile neutropenia of any grade
- anemia requiring transfusion per local or international guidelines in the absence of bleeding
- grade 5 toxicity (eg, death not due to disease progression)
- any other toxicity related to AMG 910 considered significant enough to be qualified as DLT in the opinion of the investigator, and confirmed by the DLRT, will be reported as DLT

6.2.1.4 Extension of Treatment Duration

Subjects who have shown no disease progression and no worsening of performance status at the end of cycle 6 may continue treatment for an additional 2 cycles if there are no unresolved treatment related grade 3 or 4 toxicities and if the investigator and the Amgen Medical Monitor agree that continued treatment may likely provide benefit for the subject. Further extensions of the treatment are to be agreed in the same manner at the

end of each second cycle of extended treatment. Treatment schedule and schedule of activities will be conducted as described for cycle 6.

6.2.1.5 Retreatment Group

Subjects who have derived sustained benefit from treatment, meaning at least stable disease and no worsening of performance status, for at least 3 months after the end of treatment but experience relapse or progression thereafter, and have not received any other systemic anti-cancer therapy since their last AMG 910 treatment, may be retreated in a separate retreatment group for a total of up to 2 rounds of retreatment **(up to 6 cycles each)**. Retreatment will be offered to such subjects upon agreement of the investigator and the Amgen Medical Monitor that retreatment is medically appropriate and likely to provide benefit for the subject. Subjects must meet all protocol defined inclusion and exclusion criteria and provide written consent for the retreatment (exemption: no additional test for CLDN18.2 expression in tumor tissue is required). Retreatment will be administered at the highest dose level and currently used schedule that has been assessed as safe by the DLRT at the time of retreatment initiation. Treatment schedule and schedule of activities will be conducted as described for cycles 1 through 6 in the dose exploration and expansion cohorts.

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

6.2.2.1 Amgen Investigational Product: AMG 910

The reason for any dose change of AMG 910 is to be recorded on each subject's CRF.

6.2.2.2 Infusion Interruptions/Delays/Withholding and Re-start in Case of Technical/Logistical Issues

Events leading to infusion interruption or delay for technical/logistical reasons may include: technical problem with the infusion pump or the investigational product is incorrectly prepared or administered.

Infusion Interruptions due to Technical/Logistical Issues

The administration of AMG 910 should not be interrupted, if possible. In case of infusion interruption, due to any technical or logistic reason, the interruption should be as short as possible, and the infusion continued at the earliest time possible.

In case of infusion interruption, immediately consult with Amgen Medical Monitor to determine if:

- investigational product stability is sufficient to administer the remaining infusion or
- a new infusion can be administered or
- the dose should be withheld

If the remaining infusion can be administered, no specific precautions have to be taken. If a new infusion can be administered, follow the procedures in the Schedule of Activities (Table 1-1) for the cycle day on which the original (interrupted) infusion was administered. If the infusion will need to be withheld, follow the instructions for re-start after interruptions due to adverse events described below for the next infusion.

For eIV infusions, if an infusion interruption occurs due to reasons other than adverse events (eg, technical or logistic reasons) and does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures and infusion duration will not change. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered if implemented for start of eIV infusion. If the interruption exceeds 48 hours and less than 75% of the planned 96-hour infusion has been administered, treatment with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 starting with day 1 and completion after 96 hours. If the interruption exceeds 48 hours and at least 75% of the planned 96-hour infusion has been administered, treatment will resume with the cycle 1 day 8 short-term infusion. Refer to IPIM for details of handling, preparation, and administration of eIV infusions.

Infusion Delay due to Technical/Logistical Issues

If the infusion delay was ≤ 72 hours, the dose can be administered without specific precautions. Procedures performed will follow the schedule of assessments for the cycle day on which the infusion was originally planned. The following infusions should then be administered in same dosing intervals as planned during cycles 1 and 2 or in intervals of 7 (± 1) days in case of all later dosing events; eg, if the cycle 3 day 8 infusion needs to be delayed for logistical issues, and could only be administered on day 10, the next infusion should be administered on day 17 (± 1 day) rather than the regular day 15. The ± 1-day window for dosing events after cycle 1 day 8 is allowed until the original dosing schedule is met again.

If the delay of the next infusion was > 72 hours, the dose will need to be skipped and the instructions for re-start after interruptions due to adverse events described below should be followed.

6.2.2.3 Infusion Interruptions/Delays/Withholding and Re-start due to Adverse Events

6.2.2.3.1 General Guidelines

Subjects should be assessed for toxicity before each infusion of AMG 910. The severity of the toxicity will be graded using the CTCAE version 5.0 (Section 11.4), with the exception of CRS, which must be graded using the criteria referenced in the publication by Lee et al. (Lee, et al., 2014), (see Table 6-3) and TLS, which must be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al. (Coiffier, Altman, Pui, Younes, & Cairo, 2008), (see Table 6-3). Infusion modification and dose reduction due to a toxicity will be performed according to the instructions described below and outlined in Table 6-3.

6.2.2.3.2 Infusion Interruptions due to Adverse Events

Events occurring during the infusion and requiring treatment interruption will be managed by immediate infusion interruption. The site should record any unscheduled interruption of an infusion on the electronic CRF (eCRF) and provide the start and stop date/time of the infusion.

Events requiring an infusion interruption are listed in Table 6-3.

For eIV infusions, the following adverse events should not lead to infusion interruption or delayed dosing of a next scheduled dose:

- **grade 1 or 2 CRS (including transient fever and/or vomiting [< 72 hours])**
- **grade 3 transaminitis**
- **grade 3 hypotension manageable with IV fluids or low dose vasopressor**
- **grade 3 or 4 lymphopenia resolving to grade ≤ 2 within 7 days or considered not clinically relevant**
- **isolated grade 3 fever (defined as a temperature ≥ 40°C with a duration of ≤ 24 hours) occurring outside the context of CRS**
- **laboratory parameters of grade ≥ 3, not considered clinically relevant**
- **hemoglobin ≥ 7.0 to < 8.0 g/dL if observed ≤ 7 days in the absence of bleeding signs**

6.2.2.3.3 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 6-3.

Infusion interruptions or delays for other reasons need to be discussed with the Amgen Medical Monitor.

6.2.2.3.4 Re-start of infusion

Re-starting treatment after an interruption/delay due to an adverse event or if the interruption/ delay was > 72 hours, regardless of the reason, should be performed under medical supervision**, if not already specified differently in the sections above**. The following assessments should be performed as for days 1, 2, and 3 per the Schedule of Activities for the interrupted cycle (Table 1-1):

- vital signs, pulse oximetry
- physical examination
- clinical evaluation
- weight
- ECOG Performance Status Scale
- safety labs (hematology, chemistry, coagulation, urinalysis)

The subject should be hospitalized for at least 48 hours after re-start of the infusion.

In case the interruption/delay occurred before cycle 1, day 8 and was > 72 hours, treatment restart should follow the dosing schedule and SOA for cycle 1 starting with day 1.

For eIV infusion administration: In case the interruption exceeds 48 hours and less than 75% of the planned 96-hour infusion has been administered, treatment with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 starting with day 1 and completion after 96 hours. If the interruption exceeds 48 hours and at least 75% of the planned 96-hour infusion has been administered, treatment will resume with the cycle 1 day 8 short-term infusion. Refer to IPIM for details of handling, preparation, and administration of eIV infusions.

Any premedication earlier implemented for specific dosing time points should be administered at the equivalent dosing timepoints of the treatment re-start.

6.2.2.3.5 Dose Adjustments and Re-start at a Lower Dose Level

For adverse events for which restart of treatment is allowed according to the guidelines outlined in Table 6-3, treatment may be resumed at the same or lower dose.

Re-start at a lower dose level:

For required dose reductions, follow instructions as outlined in Table 6-3.

In case more than 2 dose de-escalations are required for any reason (including but not limited to de-escalations due to the same adverse event, 2 separate adverse events, etc.), permanently discontinue treatment.

For any subject treated in cohort 1 who does not experience a DLT and who requires a dose reduction below the 6.5 μg starting dose, treatment can resume at a lower dose of 2.5 μg.

Background: The lower dose to manage patients within cohort 1 was endorsed by DLRM after the observation of a grade 2 CRS in 1 subject shortly after administration of the day 1 infusion. The subject received the C1D1 infusion at a dose of 6.5 μg according to protocol. Approximately 10 hours after the infusion the subject presented with nausea, headache, tachycardia, and liver transaminases increased up to grade 3. Also, the subject had grade 2 abdominal pain. The events recovered within 3 to 4 days with 1 dose of tocilizumab, dexamethasone, and other symptomatic treatments. The observation has not changed the benefit-risk assessment for the study and enrollment is continuing in line with treatment specifications as provided in Section 6.

Table 6-3. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation* and Management of Adverse Events Including Dose Reductions for Short-term Intravenous Infusions

Grade	Description of Severity	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Infusion-related Reaction (Short-term IV only; for eIV see Table 6-4)					
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated	n/a	Consider medication to control infusion reaction as deemed appropriate by the investigator according to local standard of care and institutional guidelines. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable Consider slowing infusion rate to deliver the dose over 90 minutes for next dose Monitoring[d] following a grade 2 event of IRR: • the subject must be monitored for all subsequent dose administrations for a duration of time that is at least as long as the time it took for the onset of the last IRR plus 4 hours or per the protocol monitoring instructions, whichever is longer. • also, considering the **2**-week treatment free period after cycles 2 and 4, the subject must be monitored for a duration of time that is at least as long as the time it took for the onset of the last IRR plus 4 hours or per the protocol monitoring instructions, whichever is longer independent of non-occurrence of events in the prior treatment This monitoring requirement should be followed until there is no reoccurrence of IRR, at which time monitoring for subsequent doses should follow per protocol post-infusion monitoring. If a subsequent IRR occurs, then the event should be managed and monitored as per protocol, i.e., until it resolves to grade ≤1.	n/a	n/a
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Immediate interruption/delay until event has improved to grade ≤ 1		• Re-start possible, if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • In case of infusion interruption, continue treatment with next scheduled infusion, do not resume prior infusion or administer delayed infusion. • Delay of the next infusion: – ≤ 72 hours: follow the **SoA** for the cycle day on which the infusion was originally planned. The next infusions should then be administered **in line with the planned dosing schedule.** – > 72 hours: **Starting with** the cycle 1 day 8 infusion and later dosing time points skip the infusion **(twice weekly dosing schedule only)** and resume **SoA** for the next scheduled infusion. • Hospitalization: at least 48 hours (see also Monitoring[d] in the Specific Management section) • Dose modification: resume at the same dose • Additional measures: additional assessments as indicated in Section 6.2.2.3.4	If not improved to ≤ grade 1 in ≤ 14 days

Page 1 of **17**

Abbreviations and footnotes defined on last page of table

Grade	Description of Severity	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Infusion-related Reaction (Short-term IV only; continued)					
3	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Immediate interruption/ delay until event has improved to grade ≤ 1	Consider supportive therapy including steroids as clinically indicated. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. Consider slowing infusion rate to deliver the dose over 90 minutes for next dose**.** Monitoring[d] following a grade 3 event of IRR: • the subject must be monitored for all subsequent dose administrations for a duration of time that is at least as long as the time it took for the onset of the last IRR plus 4 hours or per the protocol monitoring instructions, whichever is longer. • also, considering the **2**-week treatment free period after cycles 2 and 4, the subject must be monitored for a duration of time that is at least as long as the time it took for the onset of the last IRR plus 4 hours or per the protocol monitoring instructions, whichever is longer independent of non-occurrence of events in the prior treatment This monitoring requirement should be followed until there is no reoccurrence of IRR, at which time monitoring for subsequent doses should follow per protocol post-infusion monitoring. If a subsequent IRR occurs, then the event should be managed and monitored as per protocol, i.e., until it resolves to grade ≤1.	As for grade 2 infusion-related reaction, with the exception of mandatory dose modification: reduce to next lower dose level in Table 6-2 Reoccurrence: discuss restarting with Amgen Medical Monitor	If not improved to ≤ grade 1 in ≤ 14 days
4	Life-threatening consequences; urgent intervention indicated	n/a	As for grade 3 infusion-related reaction	n/a	Immediately stop the infusion (if applicable) and permanently discontinue AMG 910 therapy

Abbreviations and footnotes defined on last page of table

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome[c] (see Section 11.13 for additional guidance and grading scale details) (Short-term IV only; for eIV see Table 6-4)					
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%, 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/ delay AMG 910 until event improves to CRS grade ≤ 1. **eIV infusion: Avoid treatment interruption**	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. • If hypoxia or hypotension lasts > 24 hours manage as grade 3 CRS Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours and until resolution to CRS grade ≤ 1. Investigators should consider use of tocilizumab[c] as an additional therapy in this setting at a dose of 8 mg/kg as a single dose. For subjects with extensive co-morbidities or poor performance status, manage per grade 3 CRS guidance below. Monitoring[d] following an event of CRS: • the subject must be monitored for all subsequent dose administrations for a duration of time that is at least as long as the time it took for the onset of the last CRS plus 4 hours or per the protocol monitoring instructions, whichever is longer. • also, considering the **2**-week treatment free period after cycles 2 and 4, the subject must be monitored for dose 1 cycle 3 and dose 1 cycle 5 for a duration of time that is at least as long as the time it took for the onset of the last CRS plus 4 hours or per the protocol monitoring instructions, whichever is longer independent of non-occurrence of events in the prior treatment This monitoring requirement should be followed until there is no reoccurrence of CRS, at which time monitoring for subsequent doses should follow per protocol post-infusion monitoring. If a CRS occurs, then the event should be managed and monitored as per protocol, i.e., until it resolves to grade ≤ 1.	• Re-start possible if successfully managed and improved to ≤ grade 1 within 7 days. • Consult with Amgen Medical Monitor first. • In case of infusion interruption, continue treatment with next planned dose, do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered if implemented for start of eIV infusion.** • Delay of next infusion: – ≤ 72 hours: follow the **SoA** for the cycle day on which the infusion was originally planned. **T**he next infusions should then be administered **in line with the planned dosing schedule.** – > 72 hours: For the cycle 1 day 8 infusion and later dosing time points skip the infusion **(twice weekly dosing schedule only)** and resume **SoA** for the next scheduled infusion. • Hospitalization: at least 48 hours (see also Monitoring[d] in the Specific Management section) • Dose modification: – **After eIV infusion interruption > 24 hours restart at same or at lower dose after discussion with Amgen Medical Monitor. Refer to Section 6.2.2.3.** • **After IV interruption** reduce to next lower dose level in Table 6-2 **or discuss with Amgen Medical Monitor**. For cohort 1, follow instructions of Section 6.2.2.3.5. • Additional measures: additional assessments as indicated in Section 6.2.2.3.4	If there is no improvement to CRS ≤ grade 1 within 7 days. OR Occurrence of grade ≥ 3 CRS with any subsequent dose

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 11.13 for additional guidance and grading scale details) (Short-term IV only)					
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 910 until event improves 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. Additionally, tocilizumab[c] should be administered at a dose of 8 mg/kg as a single dose and may be repeated once within 24 to 48 hours based on clinical assessment. Monitoring[d] following an event of CRS: • the subject must be monitored for all subsequent dose administrations for a duration of time that is at least as long as the time it took for the onset of the last CRS plus 4 hours or per the protocol monitoring instructions, whichever is longer. • also, considering the **2**-week treatment free period after cycles 2 and 4, the subject must be monitored for dose 1 cycle 3 and dose 1 cycle 5 for a duration of time that is at least as long as the time it took for the onset of the last CRS plus 4 hours or per the protocol monitoring instructions, whichever is longer independent of non-occurrence of events in the prior treatment This monitoring requirement should be followed until there is no reoccurrence of CRS, at which time monitoring for subsequent doses should follow per protocol post-infusion monitoring. If a CRS occurs, then the event should be managed and monitored as per protocol, i.e., until it resolves to grade ≤ 1.	• Re-start possible if successfully managed and improved to ≤ grade 1 within 7 days. • Consult with Amgen Medical Monitor first. • In case of infusion interruption, continue treatment with next planned dose, do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: Treatment initiation with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 day 1. This should be done at the earliest after 48 hours and under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered. Refer to Section 6.2.2.3.** • Delay of next infusion: – ≤ 72 hours: follow the **SoA** for the cycle day on which the infusion was originally planned. **The next infusions should then be administered in line with the planned dosing schedule.** – > 72 hours: **Starting with** the cycle 1 day 8 infusion and later dosing time points skip the infusion **(twice weekly dosing schedule only)** and resume **SoA** for the next scheduled infusion. • Hospitalization: at least 48 hours after resolution to ≤ grade 2 (see also Monitoring[d] in the Specific Management section) • Dose modification: reduce to next lower dose level in Table 6-2 • Additional measures: additional assessments as indicated in Section 6.2.2.3.4	If there is no improvement to CRS ≤ grade 2 within 5 days and CRS ≤ grade 1 within 7 days. OR If subject is still febrile or still on vasopressors within 8 hours after initiation of corticosteroid and tocilizumab OR In case of 2 separate grade 3 CRS events.

Abbreviations and footnotes defined on last page of table

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 11.13 for additional guidance and grading scale details) (Short-term IV only)					
4	Life-threatening symptoms • Requirement for ventilator support OR • Grade 4 organ toxicity (excluding transaminitis) per CTCAE criteria		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 8 mg/kg as a single dose and may be repeated once within 24 to 48 hours based on clinical assessment.	n/a	Immediately stop the infusion (if applicable) and permanently discontinue AMG 910 therapy

Abbreviations and footnotes defined on last page of table

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Tumor Lysis Syndrome (TLS) – Grading according to Cairo-Bishop Criteria (see Section 11.14)				
2 (clinical TLS)	Immediate interruption/ delay until event has improved to grade ≤ 1	TLS should be managed according the local standard of care and institutional guidelines.	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days • Consult with Amgen Medical Monitor first. • In case of infusion interruption, continue treatment with next schedule infusion, do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered if implemented for start of eIV infusion. Refer to Section 6.2.2.3. Reduce to next lower dose level in Table 6-2. If the interruption exceeds 48 hours, treatment initiation with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 starting with day 1. Restarting due to any eIV infusion interruption should be discussed with the medical monitor.** • Delay of next infusion: – ≤ 72 hours: follow the **SoA** for the cycle day on which the infusion was originally planned. **The next infusions should then be administered in line with the planned dosing schedule.** – > 72 hours: **Starting with** the cycle 1 day 8 infusion and later dosing time points skip the infusion **(twice weekly dosing schedule only)** and resume **SoA** for the next scheduled infusion. • Hospitalization: at least 48 hours • Dose modification: reduce to next lower dose level in Table 6-2 • Additional measures: additional assessments as indicated in Section 6.2.2.3.4	If not improved to ≤ grade 1 in ≤ 14 days OR In case of repeat grade 2 TLS event despite dose reduction.

Abbreviations and footnotes defined on last page of table.

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Tumor Lysis Syndrome (TLS) – Grading according to Cairo-Bishop Criteria (see Section 11.14)				
3 (clinical TLS)	Immediate interruption/ delay until event has improved to grade ≤ 1	TLS should be managed according to the local standard of care and institutional guidelines	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days • Restart should only be considered if there is agreement between the investigator and the Amgen Medical Monitor that the patient is very likely to benefit from continued treatment. • In case of infusion interruption, continue treatment with next schedule infusion, do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered. Reduce to next lower dose level in Table 6-2. If the interruption exceeds 48 hours, treatment initiation with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 starting with day 1. Restarting due to any eIV infusion interruption should be discussed with the medical monitor. Refer to Section 6.2.2.3.** • Delay of next infusion: – ≤ 72 hours: follow the **SoA** for the cycle day on which the infusion was originally planned. **The next infusions should then be administered in line with the planned dosing schedule.** – > 72 hours: **Starting with** the cycle 1 day 8 infusion and later dosing time points skip the infusion **(twice weekly dosing schedule only)** and resume **SoA** for the next scheduled infusion. • Hospitalization: at least 48 hours • Dose modification: reduce to next lower dose level in Table 6-2 • Additional measures: additional assessments as indicated in Section 6.2.2.3.4	If not improved to ≤ grade 1 in ≤ 14 days OR In case of repeat grade ≥ 2 TLS event despite dose reduction
4 (clinical TLS)	n/a	TLS should be managed according to the local standard of care and institutional guidelines	n/a	Immediately stop the infusion (if applicable) and permanently discontinue AMG 910 therapy

Abbreviations and footnotes defined on last page of table

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Neurological events				
≥ 2	Interruption/ delay until event has improved to grade ≤ 1	Consider administration of corticosteroids (and tocilizumab if associated with CRS). Following a seizure: administer anti-seizure medication according to the local standard of care and institutional guidelines	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • In case of infusion interruption, continue treatment with next scheduled infusion, do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered. If the interruption exceeds 48 hours, treatment initiation with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 starting with day 1. Restarting due to any eIV infusion interruption should be discussed with the medical monitor. Refer to Section 6.2.2.3.** • Delay of next infusion: – ≤ 72 hours: follow the **SoA** for the cycle day on which the infusion was originally planned. **The next infusions should then be administered in line with the planned dosing schedule.** – > 72 hours: **Starting with** the cycle 1 day 8 infusion and later dosing time points skip the infusion **(twice weekly dosing schedule only)** and resume **SoA** for the next scheduled infusion. • Hospitalization: at least 48 hours • Dose modification for grade 2: resume at the same dose • Dose modification for grade ≥ 3: resume at next lower dose • Additional measures: additional assessments as indicated in Section 6.2.2.3.4	If grade 4 event OR In case of more than 1 seizure OR If resolution or improvement to ≤ grade 1 in > 14 days OR In case of repeat ≥ grade 2 event

Abbreviations and footnotes defined on last page of table

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Gastrointestinal events: Nausea				
1 **to** 2	If symptomatic ≥ 5 days	• Treat symptomatically • If symptoms < 5 days, and symptoms **grade** 1 **to** 2, continue investigational product	• Resolved or improved to grade ≤ 1 or baseline in 5 days ○ Dose Modification: Resume at same dose • Reoccurrence: Resolved or improved to grade ≤ 1 or baseline in 5 days ○ Dose Modification: Resume at same dose	If not returned to grade ≤ 1 or baseline in 5 days after interruption
3	Interrupt	• Consider tube feed/TPN • Consider GI consult • Other medical interventions as clinically indicated and per institutional guidelines	• Resolved or improved to grade ≤ 2 in 48 hours • Re-start with next scheduled infusion, do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered (Table 6-2). If the interruption exceeds 48 hours, treatment initiation with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 starting with day 1. Restarting due to any eIV infusion interruption should be discussed with the medical monitor. Refer to Section 6.2.2.3.** ○ Dose Modification: Resume at same dose • **Second** event reoccurrence: Resolved or improved to grade ≤ 2 in 48 hours ○ Dose Modification: consider next lower dose at investigator's discretion • Subsequent event occurrence: Re-start possible after discussion with Amgen Medical Monitor ○ Dose Modification: Resume at same dose or reduce to next lower dose level • **Second** event that requires TPN or feeding tube can only be re-started following discussion with the Amgen Medical Monitor	If not returned to grade ≤ 2 in 48 hours after interruption

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Gastrointestinal events: Vomiting				
1	If deemed intolerable by the subject or investigator and not responding to appropriate medical management or if symptomatic ≥ 5 days	• Treat symptomatically • If symptoms persist ≥ 48 hours after treatment interruption, consider GI consult and discuss with Amgen Medical Monitor	• Re-start with next scheduled infusion, do not resume prior infusion or administer delayed infusion • Dose Modification: Resume at same dose	Not applicable
2	If deemed intolerable by the subject or investigator and not responding to appropriate medical management or if symptomatic ≥ 5 days	• IV hydration • Other medical interventions as clinically indicated and per institutional guidelines • Reoccurrence of event: Same management and GI consult	• Resolved or improved to grade ≤ 1 in 48 hours o Dose Modification: Resume at same dose • Re-start with next scheduled infusion, do not resume prior infusion or administer delayed infusion • **Second** event occurrence: Resolved or improved to grade ≤ 1 in 48 hours o Dose Modification: Consider lower dose at investigator's discretion • Subsequent event occurrence: Re-start possible after discussion with Amgen Medical Monitor o Dose Modification: Per discussion with Amgen Medical Monitor	If not returned to grade ≤ 1 in 48 hours after interruption
3	Interrupt	• Tube feed/TPN • Other medical interventions as clinically indicated and per institutional guidelines • Reoccurrence of event: Same management and GI consult	• Resolved or improved to grade ≤ 1 in 48 hours o Dose Modification: Resume at same dose • Re-start with next scheduled infusion do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered. If the interruption exceeds 48 hours, treatment initiation with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 starting with day 1. Restarting due to any eIV infusion interruption should be discussed with the medical monitor. Refer to Section 6.2.2.3.** • **Second** event occurrence: Resolved or improved to grade ≤1 in 48 hours o Dose Modification: Consider next lower dose at investigator's discretion • Subsequent event occurrence: Re-start possible after discussion with Amgen Medical Monitor o Dose Modification: Per discussion with Amgen Medical Monitor • **Second** event that requires TPN or feeding tube can only be re-started following discussion with the Amgen Medical Monitor	If not returned to grade ≤ 1 in 48 hours after interruption
4	Interrupt	• Hospitalization for tube feeding/ TPN • Other medical interventions as clinically indicated and per institutional guidelines • GI consult	• Re-start possible at next lower dose if resolved or improved to grade ≤ 1 in 72 hours following discussion with GI consult and Amgen Medical Monitor • Re-start with next scheduled infusion, do not resume prior infusion or administer delayed infusion • **Second** event that require TPN or feeding tube can only be re-started following discussion with the Amgen Medical Monitor	If not returned to grade ≤ 1 in 72 hours after interruption OR After **second** occurrence of a grade 4 event after restart of investigational product

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Gastrointestinal events: Abdominal pain				
1 **to** 2	If deemed intolerable by the subject or investigator and not responding to appropriate medical management	• Treat as clinically indicated • Other medical interventions as clinically indicated and per institutional guidelines • If symptomatic ≥ 24 hours, consider GI consult, consider upper GI endoscopy • Reoccurrence of event: Same management	• Resolved or improved to grade ≤ 1 or baseline in 48 hours ○ Dose Modification: Resume at same dose • Re-start with next scheduled infusion, do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered. Refer to Section 6.2.2.3.** • **Second** event occurrence: Resolved or improved to grade ≤ 1 in 24 hours ○ Dose Modification: Re-start at next lower dose in Table 6-2 • Subsequent event occurrence: Re-start possible after discussion with Amgen Medical Monitor ○ Dose Modification: Per discussion with Amgen Medical Monitor	If not returned to grade ≤ 1 or baseline in 48 hours after interruption If abnormal GI pathology distant from original tumor per GI consult For abdominal pain indicative of gastritis, gastric hemorrhage, gastric perforation or fistula, refer to events listed in table for guidance
3	Interrupt	• Treat as clinically indicated • Other medical interventions as clinically indicated and per institutional guidelines • If symptomatic ≥ 24 hours, consider GI consult, consider upper GI endoscopy • Reoccurrence of event: Same management	• Resolved or improved to grade ≤ 1 or baseline in 24 hours ○ Dose Modification: Re-start at next lower dose in Table 6-2 • Re-start with next scheduled infusion, do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered. Reduce to next lower dose level in Table 6-2.** • **Second** event occurrence: Resolved or improved to grade ≤ 1 in 24 hours ○ Dose Modification: Restart at next lower dose in Table 6-2 • Subsequent event occurrence: Re-start possible after discussion with Amgen Medical Monitor	If not returned to grade ≤ 1 or baseline in 24 hours after interruption If abnormal GI pathology distant from original per GI consult or endoscopy For abdominal pain indicative of gastritis, gastric hemorrhage, gastric perforation or fistula, refer to these events listed in table for guidance

Abbreviations and footnotes defined on last page of table

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Gastrointestinal events: Gastritis				
1	If deemed intolerable by the subject or investigator and not responding to appropriate medical management	• Treat as clinically indicated	• Re-start with next scheduled infusion, do not resume prior infusion or administer delayed infusion • Dose Modification: Resume at same dose	Not applicable
2	If deemed intolerable by the subject or investigator and not responding to appropriate medical management until event has improved to grade ≤ 1	• Treat as clinically indicated • Other medical interventions as clinically indicated and per institutional guidelines • Consider GI consult • Reoccurrence of event: Same management	• Resolved or improved to grade ≤ 1 in 72 hours, re-start at next lower dose if there is agreement per GI consult and following discussion with Amgen Medical Monitor • Re-start with next scheduled infusion, do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered. If the interruption exceeds 48 hours, treatment initiation with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 starting with day 1. Restarting due to any eIV infusion interruption should be discussed with the medical monitor. Refer to Section 6.2.2.3.** • **Second** event occurrence: Re-start possible at next lower dose if resolved or improved to grade ≤ 1 in 72 hours, and there is agreement per GI consult and following discussion with Amgen Medical Monitor	If reoccurrence of grade 2 event and symptoms persists > 72 hours
3	Permanent discontinuation	• Medical evaluation, assessment • Hospitalization • Consider TPN/tube feed • GI consult including upper GI endoscopy • Reoccurrence of event: Same management	• Not applicable	Permanent discontinuation
4	Permanent discontinuation	• Treat as clinically indicated • Hospitalization • Consider TPN/tube feed • GI consult including upper GI endoscopy • Other medical interventions as clinically indicated and per institutional guidelines	• Not applicable	Permanent discontinuation

Grade	Interruption/Delay	Specific Management	Re-start Guidance	Permanent Discontinuation
Gastrointestinal events: Gastric hemorrhage				
1	If event reoccurs, interrupt	• Medical evaluation/ assessment, and treatment as clinically indicated • GI consult • Reoccurrence of event: Same management	• Re-start possible at next lower dose if symptoms resolved in 7 days (no active bleeding), and following discussion with Amgen Medical Monitor • Re-start treatment with next scheduled infusion, do not resume prior infusion or administer delayed infusion • **Second** event occurrence: Re-start possible at next lower dose if symptoms resolved in 7 days (no active bleeding) and following discussion with Amgen Medical Monitor • **Third** event occurrence: Re-start possible at next lower dose if symptoms resolved in 7 days (no active bleeding), and following discussion with Amgen Medical Monitor	If symptoms persists > 7 days OR If a **fourth** occurrence of event after restart of investigational product OR Occurrence of grade ≥ 3 gastric hemorrhage with any subsequent dose
2	Interrupt	• Medical evaluation/ assessment, and treatment as clinically indicated • GI consult • Consider endoscopy • Reoccurrence of event: Same management	• Re-start possible at next lower dose if symptoms resolved to grade ≤ 1 in 7 days (no active bleeding), and following discussion with Amgen Medical Monitor • Re-start with next scheduled infusion, do not resume prior infusion or administer delayed infusion • **Second** event occurrence: Re-start possible at next lower dose if symptoms resolved in 7 days (no active bleeding), and following discussion with Amgen Medical Monitor • **Second** event that requires TPN or feeding tube can only be re-started following discussion with the Amgen Medical Monitor	If symptoms persists > 7 days OR Occurrence of grade ≥ 3 gastric hemorrhage with any subsequent dose
3	Permanent discontinuation	• Medical evaluation, assessment • Hospitalization • Consider TPN/tube feed • GI consult including upper GI endoscopy • Reoccurrence of event: Same management	Not applicable	Permanent discontinuation
4	Permanent discontinuation	• Other medical interventions as clinically indicated and per institutional guidelines • Endoscopy	Not applicable	Permanent discontinuation

Abbreviations and footnotes defined on last page of table

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Gastrointestinal events: Gastric perforation or fistula				
2 **to** 3	Permanent discontinuation	• Emergent medical evaluation/ assessment, and treatment as clinically indicated • GI consult • Other medical interventions as clinically indicated and per institutional guidelines	Not applicable	Permanent discontinuation
4	Permanent discontinuation	• Urgent intervention indicated • GI consult • Other medical interventions as clinically indicated and per institutional guidelines	Not applicable	Permanent discontinuation

Page 14 of **17**

Abbreviations and footnotes defined on last page of table

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Any other events not meeting DLT criteria				
≥ 3	Interruption/delay required if deemed intolerable and/or clinically significant by the subject or investigator and not responding to appropriate medical management until event has improved to grade ≤ 1	n/a	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • In case of infusion interruption, continue treatment with next scheduled infusion, do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered. If the interruption exceeds 48 hours, treatment initiation with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 starting with day 1. Restarting due to any eIV infusion interruption should be discussed with the medical monitor.** • Delay of next infusion: – ≤ 72 hours: follow the **SoA** for the cycle day on which the infusion was originally planned. **The next infusions should then be administered in line with the planned dosing schedule.** – > 72 hours: **Starting with** the cycle 1 day 8 infusion and later dosing time points skip the infusion **(twice weekly dosing schedule only)** and resume **SoA** for the next scheduled infusion. • Hospitalization: at least 48 hours • Dose modification: reduce to next lower dose level in Table 6-2 • Additional measures: additional assessments as indicated in Section 6.2.2.3.4	If not improved to ≤ grade 1 in ≤ 14 days. OR In case of reappearance of same event at grade 4 OR In case of repeat grade ≥ 3 event despite dose reduction

Abbreviations and footnotes defined on last page of table

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Any Non-AMG 910-related events				
4	Interruption/ delay required if deemed intolerable by the subject or investigator and not responding to appropriate medical management until event has improved to grade ≤ 1	n/a	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 28 days. • In case of infusion interruption, continue treatment with next scheduled infusion, do not resume prior infusion or administer delayed infusion. **For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered. If the interruption exceeds 48 hours, treatment initiation with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 starting with day 1. Restarting due to any eIV infusion interruption should be discussed with the medical monitor. Refer to Section 6.2.2.3.** • Delay of next infusion: – ≤ 72 hours: follow the **SoA** for the cycle day on which the infusion was originally planned. **The next infusions should then be administered in line with the planned dosing schedule.** – > 72 hours: **Starting with** the cycle 1 day 8 infusion and later dosing time points skip the infusion **(twice weekly dosing schedule only)** and resume **SoA** for the next scheduled infusion. • Hospitalization: at least 48 hours • Dose modification: If AMG 910 is resumed then the AMG 910 dose will be reduced to the next lower dose level in Table 6-2 after discussion with Amgen Medical Monitor • Additional measures: additional assessments as indicated in Section 6.2.2.3.4	If not improved to ≤ grade 1 in ≤ 28 days. OR In case of reappearance of same event at grade 4
Hepatotoxicity				
For Stopping and Rechallenge Rules please refer to Section 11.7.				

Abbreviations and footnotes defined on last page of table

CRS = cytokine release syndrome**;** CTCAE = Common Terminology Criteria for Adverse Events**; DLT = dose-limiting toxicity; eIV = extended intravenous;** GI = gastrointestinal**; IRR = infusion-related reaction;** IV = intravenous; MTD = maximum tolerated dose; NSAID = non-steroidal anti-inflammatory drug; Q2 = every 2**; SoA = Schedule of Activities; TLS = tumor lysis syndrome;** TPN = total parenteral nutrition**.**

[a] Revised grading system for CRS (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 2 doses of tocilizumab per study subject

[d] Eg, If a subject experiences an IRR or CRS that started 3 days after the cycle 1 day **8** dose, this subject should be monitored for at least 3 days plus 4 hours post-infusion for subsequent doses until the subject no longer has IRR or CRS events. **If a subject experiences IRR or CRS that started 1 day after the cycle 1 day 8 dose, this subject can be monitored for 48 hours post-infusion for subsequent doses until the subject no longer has IRR or CRS events.**

***Note: In specifically defined situations, a restart at a next lower dose level can be taken into consideration but only if all additional requirements for restart as stated in Section 7.1 apply.**

Table 6-4. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation* and Management of Infusion-related Reactions Including Dose Reductions During Extended Intravenous (eIV) Infusions

Grade	Description of Severity	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated	n/a	Consider medication to control infusion reaction as deemed appropriate by the investigator according to local standard of care and institutional guidelines. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable Monitoring[d] following a grade 2 event of IRR: • the subject must be monitored for all subsequent dose administrations (re-start and dosing thereafter) for a duration of time that is at least as long as the time it took for the onset of the last IRR plus 4 hours or per the protocol monitoring instructions, whichever is longer. • also, considering initiation after the 2-week treatment free period after cycles 2 and 4, the subject must be monitored for a duration of time that is at least as long as the time it took for the onset of the last IRR plus 4 hours or per the protocol monitoring instructions, whichever is longer independent of non-occurrence of events in the prior treatment This monitoring requirement should be followed until there is no reoccurrence of IRR, at which time monitoring for subsequent doses should follow per protocol post-infusion monitoring. If a subsequent IRR occurs, then the event should be managed and monitored as per protocol, i.e., until it resolves to grade ≤1.	n/a	n/a
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Immediate interruption/delay until event has improved to grade ≤ 1		• Re-start possible, if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • Delay of re-start: – Re-start 7 days from cycle 1 day 1 at earliest – Follow the SoA from cycle 1 day 1 onwards – Hospitalization: at least 48 hours (see also Monitoring in the Specific Management section) • Dose modification: resume at the same dose • For next short-term infusion after the eIV part consider slowing infusion rate to deliver the dose over 90 minutes • Additional measures: additional assessments as indicated in Section 6.2.2.3.4	If not improved to ≤ grade 1 in ≤ 14 days If event re-occurs at higher grade

Abbreviations and footnotes defined on last page of table

Grade	Description of Severity	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Infusion-related Reaction (eIV; continued)					
3	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Immediate interruption	Consider supportive therapy including steroids as clinically indicated. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. Monitoring following a grade 3 event of IRR: • the subject must be monitored for all subsequent dose administrations for a duration of time that is at least as long as the time it took for the onset of the last IRR plus 4 hours or per the protocol monitoring instructions, whichever is longer. • also, considering the 2-week treatment free period after cycles 2 and 4, the subject must be monitored for a duration of time that is at least as long as the time it took for the onset of the last IRR plus 4 hours or per the protocol monitoring instructions, whichever is longer independent of non-occurrence of events in the prior treatment This monitoring requirement should be followed until there is no reoccurrence of IRR, at which time monitoring for subsequent doses should follow per protocol post-infusion monitoring. If a subsequent IRR occurs, then the event should be managed and monitored as per protocol, i.e., until it resolves to grade ≤1.	A restart needs to be discussed with Amgen Medical Monitor and should only be taken into consideration after careful risk-benefit assessment Mandatory dose modification: reduce to next lower dose level in Table 6-2 All other re-start instructions as for grade 2 infusion-related reaction, apply For short-term infusions after the eIV part • consider slowing infusion rate to deliver the next dose over 90 minutes • reduce dose to next lower dose level in Table 6-2	If not improved to ≤ grade 1 in ≤ 14 days Re-occurrence of a grade 3 event
4	Life-threatening consequences; urgent intervention indicated	n/a	As for grade 3 infusion-related reaction	n/a	Immediately stop the infusion (if applicable) and permanently discontinue AMG 910 therapy

Abbreviations and footnotes defined on last page of table

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome[c] (see Section 11.13 for additional guidance and grading scale details) (eIV)					
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%, 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/ delay AMG 910 until event improves to CRS grade ≤ 1. eIV infusion: Avoid treatment interruption	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. • If hypoxia or hypotension lasts > 24 hours manage as grade 3 CRS Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours and until resolution to CRS grade ≤ 1. Investigators should consider use of tocilizumab[c] as an additional therapy in this setting at a dose of 8 mg/kg as a single dose. For subjects with extensive co-morbidities or poor performance status, manage per grade 3 CRS guidance below. Monitoring[d] following an event of CRS: • the subject must be monitored for all subsequent dose administrations for a duration of time that is at least as long as the time it took for the onset of the last CRS plus 4 hours or per the protocol monitoring instructions, whichever is longer. This monitoring requirement should be followed until there is no reoccurrence of CRS, at which time monitoring for subsequent doses should follow per protocol post-infusion monitoring. If a CRS occurs, then the event should be managed and monitored as per protocol, ie, until it resolves to grade ≤ 1.	• Re-start possible if successfully managed and improved to ≤ grade 1 within 7 days. • Consult with Amgen Medical Monitor first. • In case of infusion interruption, continue treatment with next planned dose, do not resume prior infusion or administer delayed infusion. For eIV infusion administration: In case the interruption does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered if implemented for start of eIV infusion. • Delay of next infusion: – ≤ 72 hours: follow the SoA for the cycle day on which the infusion was originally planned. The next infusions should then be administered in line with the planned dosing schedule. – > 72 hours: For the cycle 1 day 8 infusion and later dosing time points skip the infusion (twice weekly dosing schedule only) and resume SoA for the next scheduled infusion. • Hospitalization: at least 48 hours (see also Monitoring[d] in the Specific Management section) • Dose modification: – After eIV infusion interruption > 24 hours restart at same or at lower dose after discussion with Amgen Medical Monitor • After IV interruption reduce to next lower dose level in Table 6-2 or discuss with Amgen Medical Monitor. For cohort 1, follow instructions of Section 6.2.2.3.5. • Additional measures: additional assessments as indicated in Section 6.2.2.3.4	If there is no improvement to CRS ≤ grade 1 within 7 days. OR Occurrence of grade ≥ 3 CRS with any subsequent dose

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 11.13 for additional guidance and grading scale details) (eIV)					
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 910 until event improves 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. Additionally, tocilizumab[c] should be administered at a dose of 8 mg/kg as a single dose and may be repeated once within 24 to 48 hours based on clinical assessment. Monitoring following an event of CRS: • the subject must be monitored for all subsequent dose administrations for a duration of time that is at least as long as the time it took for the onset of the last CRS plus 4 hours or per the protocol monitoring instructions, whichever is longer. This monitoring requirement should be followed until there is no reoccurrence of CRS, at which time monitoring for subsequent doses should follow per protocol post-infusion monitoring. If a CRS occurs, then the event should be managed and monitored as per protocol, i.e., until it resolves to grade ≤ 1.	• Re-start possible if successfully managed and improved to ≤ grade 1 within 7 days. • Consult with Amgen Medical Monitor first. • In case of infusion interruption, continue treatment with next planned dose, do not resume prior infusion or administer delayed infusion. For eIV infusion administration: Treatment initiation with eIV infusion should be restarted following the dosing schedule and SoA for cycle 1 day 1. This should be done at the earliest after 48 hours and under the supervision of the investigator or designee and premedication as described in Section 6.1.4 should be administered. • Delay of next infusion: – ≤ 72 hours: follow the SoA for the cycle day on which the infusion was originally planned. The next infusions should then be administered in line with the planned dosing schedule. – > 72 hours: Starting with the cycle 1 day 8 infusion and later dosing time points skip the infusion (twice weekly dosing schedule only) and resume SoA for the next scheduled infusion. • Hospitalization: at least 48 hours after resolution to ≤ grade 2 (see also Monitoring[d] in the Specific Management section) • Dose modification: reduce to next lower dose level in Table 6-2 • Additional measures: additional assessments as indicated in Section 6.2.2.3.4	If there is no improvement to CRS ≤ grade 2 within 5 days and CRS ≤ grade 1 within 7 days. OR If subject is still febrile or still on vasopressors within 8 hours after initiation of corticosteroid and tocilizumab OR In case of 2 separate grade 3 CRS events.

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 11.13 for additional guidance and grading scale details) (eIV)					
4	Life-threatening symptoms • Requirement for ventilator support OR • Grade 4 organ toxicity (excluding transaminitis) per CTCAE criteria		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 8 mg/kg as a single dose and may be repeated once within 24 to 48 hours based on clinical assessment.	n/a	Immediately stop the infusion (if applicable) and permanently discontinue AMG 910 therapy

CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; eIV = extended intravenous; IRR = infusion-related reaction; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug; Q2 = every 2; SoA = Schedule of Activities; TLS = tumor lysis syndrome.

[a] Revised grading system for CRS (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 2 doses of tocilizumab per study subject.

*Note: In specifically defined situations, a restart at a next lower dose level can be taken into consideration but only if all additional requirements for restart as stated in Section 7.1 apply.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

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

6.3 Preparation/Handling/Storage/Accountability

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

6.4 Treatment Compliance

AMG 910 will be administered at the study center by a qualified staff member. A physician must be available at the time of administration of investigational product. Information regarding investigational product administration including date, time, dose, start and stop time of infusion, and other essential information are to be recorded on the individual subject's Investigational Product Administration CRF per the CRF completion guidelines. Please refer to IPIM for more details on treatment compliance of AMG 910.

6.5 Treatment of Overdose

As the maximum recommended dose is not assessed yet, the effects of overdose of this product are not known.

The administered AMG 910 dose may be up to 10% lower or higher than specified in the protocol. A dose of up to 10% higher than the intended dose may not require specific intervention.

In any case of overdose, 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 11.4.

A dose of > 10% higher than the intended AMG 910 dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 11.4.

6.6 Prior and Concomitant Treatment

6.6.1 Prior Treatment

Prior therapies that were taken/used from 3 months prior to signing informed consent will be collected. Collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

For all prior therapies taken for gastric cancer (eg, chemotherapy or treatment with TKI), collect (in the order they were administered):

- therapy name
- indication
- dose and schedule of the agent(s)
- unit
- frequency
- start and stop dates
- disease state in which it was administered
- type of progression (radiographic, and/or symptomatic)
- response (resistant versus sensitive): categorized on the basis of the post-therapy radiographic change pattern for agents that reduce tumor burden

Additionally, details of the dates, portals, and total administered dose by portal should be recorded for all courses of radiation therapy, including those directed at the primary and metastatic site(s).

6.6.2 Concomitant Treatment

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

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

For concomitant therapies being taken for the disease under study, collect therapy name, indication, dose, unit, frequency, start and stop dates. For all other concomitant therapies, collect therapy name, indication, dose, start and stop dates.

6.6.2.1 Supportive Care

Subjects can receive supportive care according to local guidelines for blood product support, antibiotics, antivirals, analgesics, etc. Details of supportive care measures should be recorded for all patients.

6.6.2.2 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.

6.6.2.3 Tumor Lysis Syndrome

While rare in gastric cancer, TLS is a severe, life-threatening disorder that can occur in highly proliferative malignancies or with debulking of extensive tumor burden. 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 lactate dehydrogenase, 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 Table 6-3.

To prevent TLS, before administration of AMG 910 all subjects should receive at the discretion of the investigator appropriate hydration and supportive measures according to local standard of care and institutional guidelines. Monitor for evidence of TLS during treatment and manage promptly including interruption of AMG 910 infusion as outlined in Table 6-3. 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.

6.6.2.4 Nausea, Vomiting, and Diarrhea

The causes of nausea, vomiting, and diarrhea in subjects with cancer can be multifactorial. Therefore, a careful assessment which includes a detailed history, physical examination, and investigations for causes is vital. Management of nausea,

vomiting, and diarrhea should be tailored to the individual subject's clinical situation and endoscopic evaluations should be taken in consideration.

6.6.2.4.1 Nausea and Vomiting

Antiemesis prophylaxis may be given according to local standard of care institutional standards if clinically indicated at the investigator's discretion. Treatment of nausea and vomiting with antiemetics such as metoclopramide should be considered according to the local standard of care and institutional guidelines. In cases with nausea and vomiting lasting for ≥ 24 hours, additional treatment with corticosteroids (dexamethasone or prednisolone) should be considered depending on tolerability/duration of previous dexamethasone administration. In case nausea and vomiting are associated with abdominal pain or any indication of bleeding, gastroscopy and AMG 910 interruption as detailed in Table 6-3 are mandated.

6.6.2.4.2 Diarrhea

All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid, and electrolytes should be substituted via IV infusion. Consider endoscopy to confirm or rule out colitis.

Treatment with loperamide (starting dose of 4 mg, followed by 2 mg every 2 hours) should start after occurrence of the first episode of diarrhea. In cases with diarrhea lasting for > 24 hours, additional treatment with corticosteroids (budesonide, dexamethasone or prednisolone) should be considered depending on tolerability/duration of previous dexamethasone administration. Additional work-up and/or GI consultation may be considered, as needed.

7. Discontinuation Criteria

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

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 7.1, 7.2, and 7.2.1.

7.1 Discontinuation of Study Treatment

Subjects 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 Table 1-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Pregnancy
- No longer clinically benefitting (may include clinical deterioration, disease or therapy related) or need for a change in systemic therapy
- A DLT leads to permanent discontinuation unless the following criteria apply, in which case a restart of treatment at the next lower dose level in Table 6-2 is allowed **or criteria per Table 6-3 apply**:

  The adverse event (including relevant lab values) is reversible and improves to grade ≤ 1 or baseline within 7 days

  The patient is experiencing clinical benefit as assessed by the investigator

There is agreement between the investigator and the Amgen Medical Monitor that treatment may be restarted

The subject gives written informed consent to continue treatment after the investigator has led an appropriate discussion of potential risks and benefits with the subject

7.2 Discontinuation From the Study

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

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Table 1-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

7.3 Lost to Follow-up

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

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

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

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 1-1).

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.

All assessments including clinical evaluation and laboratory assessments should be done in line with the requested observation periods after AMG 910 administrations as outlined in the Schedule of Activities (Table 1-1).

8.1 General Study Periods

8.1.1 Screening, Enrollment and/or Randomization

The procedures to be completed during screening are indicated in the Schedule of Activities (Table 1-1). 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 ICF, the site will register the subject manually and screen the subject in order to assess eligibility for participation. The screening window is up to 21 days. If CT and/or magnetic resonance imaging (MRI) is done prior to ICF

signature results can be used if the subject allows its use and assessments are done within 30 days of cycle 1 day 1.

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

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening 1 time. If CLDN18.2 test results come back delayed the subject does not count as screen fail and all screening results are accountable to judge on subject enrollment if treatment can start within 30 days from ICF signature.

Rescreen subjects must first be registered as screen failures 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 and all screening procedures, including informed consent, must be repeated. If planned cycle 1 day 1 is within 21 days after the original signing of the ICF, only vital signs, clinical and safety lab evaluations need to be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-1). On-study visits may be completed within ± 1 day during cycles 1 and 2 and within ± 3 days cycle 3 onwards. 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. Assessments are done pre-infusion unless otherwise specified in the Schedule of Activities.

8.1.3 Safety Follow-up

The procedures to be completed during safety follow-up are indicated in the Schedule of Activities (Table 1-1). Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+3) days after the last dose of investigational product.

8.1.4 Long-term Follow-up

The procedures to be completed during long-term follow-up are indicated in the Schedule of Activities (Table 1-1). Long-term follow-up will be conducted every 6 months up to 2 years from the first dose of AMG 910 for all subjects who have not

withdrawn consent by clinic visit, telephone or chart review to assess for survival and/or the commencement of subsequent cancer therapy. **Subjects who remain on the treatment for more than 2 years do not need to have additional long-term follow-up (LTFU). They will complete the study 30 (+3) days following discontinuing treatment.**

8.1.5 End of Study

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

8.2 Description of General Study Assessments and Procedures

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

8.2.1 General Assessments

8.2.1.1 Informed Consent

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

8.2.1.2 Demographics

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

8.2.1.3 Medical History

The investigator or designee will collect a complete medical and surgical history that starts 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. Record all findings on the medical history CRF.
In addition to the medical history above, gastric cancer history must date back to the original diagnosis. The current toxicity grade will be collected for each condition that has not resolved.

8.2.1.4 Physical Examination

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

8.2.1.5 Neurological Examination

If clinically indicated, subjects will be specifically queried for neurological symptoms observed in the interval since the last extended neurological examination. Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion).

The individual performing the neurological examination will characterize the findings as either normal or abnormal. Abnormal findings found predose will be reported on the medical history page of the CRF. Abnormal findings found after the subject is dosed will be reported on the Event page of the CRF.

should be recorded on the appropriate CRF (eg, medical history, event).

8.2.1.6 Gastroscopy

Endoscopic evaluation of the upper digestive system including esophagus, stomach and first part of the small intestine according to local standards will be done as scheduled in Table 1-1 and after occurrence of toxicity observations as detailed in Table 6-3 (eg, pain in the upper abdomen, vomiting, bleeding). In addition, non-tumor stomach tissue obtained by biopsy during the gastroscopy will be evaluated by the local pathologist for abnormal findings (eg, unusual redness, ulcerative lesions, bleeding, blockages or other abnormalities). The macroscopic and microscopic examinations reports will provide characterization of the findings as either normal or abnormal. Abnormal findings found predose will be reported on the medical history page of the CRF. Abnormal findings found after the subject is dosed will be reported on the Event page of the CRF.

8.2.1.7 Physical Measurements

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

8.2.1.8 Performance Status

The subject's performance status will be assessed using the ECOG Performance Status Scale (see Section 11.10).

8.2.2 Efficacy Assessments

Efficacy will be determined by both clinical laboratory values and radiographic assessments (as outlined in Section 3).

Radiographic Assessments

Radiographic assessments will be obtained as scheduled in Table 1-3 irrespective of cycle duration including dose delays and treatment discontinuation.
Standard radiological assessments should take place until clinically significant disease progression or deterioration, withdrawal of consent, or start of new anticancer therapy. Every assessment must include contrast-enhanced CT of the chest, abdomen, pelvis, and all other known sites of disease. The assessment should include MRI of the brain if a subject has signs or symptoms suggestive of CNS metastases. The assessment can be conducted earlier if clinical deterioration necessitates an earlier scan at the discretion of the managing physician. The same contrast and modality used at screening should be used for all subsequent assessments.
Tumor burden assessments will be performed based on RECIST 1.1 and iRECIST. RECIST 1.1 criteria will be used to determine eligibility based on the investigator's review of the radiographic data. Although tumor assessments following RECIST 1.1 will continue through the first disease progression (PD), iRECIST will be used and documented in eCRF to account for unique tumor response characteristics observed with immunotherapies and enable treatment decisions beyond progression (per RECIST 1.1). Tumor burden assessment performed at sites for decisions on treatment continuation will be based on iRECIST only and will continue until immune Confirmed Progression Disease (iCPD). Tumor burden assessments by the central core laboratory will be based on RECIST 1.1 and iRECIST. To confirm disease progression, a second CT scan must be performed 4-8 weeks after the first detection of radiographical progression. Responses (partial response [PR] and complete response [CR]) require confirmation by a repeat consecutive assessment at least 4 weeks after the first detection of radiographical response. Refer to the imaging manual for details on imaging assessments.

8.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 1-1).

8.2.3.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate/pulse, 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 CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

After each AMG 910-infusion for the first 2 cycles and after the first 2 infusions of cycle 3 **and after start of eIV infusion on cycle 1 day 1**, but only while the patient is hospitalized or under observation post AMG 910 infusion, vital signs should be assessed accordingly during the following timepoints:

Short-term IV infusion:

- every 15 minutes during infusion and during first 2 hours after end of infusion (EOI)
- every 30 minutes from 2 to 4 hours EOI
- every hour from 4 to 8 hours EOI
- every 2 hours from 8 to 12 hours EOI
- every 6 hours from 12 to 24 hours EOI
- after 24 hours EOI, vital signs should be assessed per institutional standards

Extended IV infusion:

- 15 minutes after start of eIV infusion
- every 30 minutes thereafter during the first 2 hours after start of eIV infusion
- every 1 hour during hours 3 to 6 after start of eIV infusion
- every 2 hours during hours 7 to 12 after start of eIV infusion
- every 6 hours during hours 13 to 24 after start of eIV infusion
- after 24 hours after start of eIV infusion vital signs should be assessed per institutional standards

8.2.3.2 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. After each AMG 910 infusion for the first 2 cycles and after the first 2 infusions of cycle 3 **and after start of eIV infusion on cycle 1 day 1**, but only while the patient is hospitalized or under observation post AMG 910 infusions, pulse oximetry should be assessed accordingly during the following timepoints:

Short-term IV Infusion:

- Every 15 minutes during infusion and during first 2 hours after end of infusion (EOI)
- Every 30 minutes from 2 to 4 hours after EOI
- Every hour from 4 to 8 hours after EOI
- Every 2 hours from 8 to 12 hours after EOI
- Every 6 hours from 12 to 24 hours after EOI
- After 24 hours EOI, pulse oximetry should be assessed per institutional standards

Extended IV infusion:

- **15 minutes after start of eIV infusion**
- **every 30 minutes thereafter during the first 2 hours after start of eIV infusion**
- **every 1 hour during hours 3 to 6 after start of eIV infusion**
- **every 2 hours during hours 7 to 12 after start of eIV infusion**
- **every 6 hours during hours 13 to 24 after start of eIV infusion**
- **after 24 hours after start of eIV infusion vital signs should be assessed per institutional standards**

8.2.3.3 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 (all 3 ECGs should be completed within a total of five minutes from the start of the first to the completion of the third), prior to blood draws or other invasive procedures. If it is necessary to schedule blood draws for the predose timepoints (see Section 1.3, Schedule of Activities) before the ECG to allow for timely administration of investigational product, blood draws should be performed at least 60 minutes before the ECG. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

- For screening: triplicate ECGs
- For cycle 1: ≥ 3 baseline ECGs collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (all 3 ECGs should be completed within a total of five minutes from the start of the first to the completion of the third) (total 9 ECGs)

- For cycle 1: triplicate ECGs at time points after dosing
- For cycle 2 and beyond: single ECGs may be collected per time point

Baseline is defined as the pre-dose assessment on cycle 1 day 1. The investigator or designated site clinician will review all ECGs. **Electrocardiograms may** be transferred electronically to an ECG central reader for analysis per Amgen instructions. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Standard ECG machines should be used for all study-related ECG requirements.

8.2.3.4 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.

8.2.4 Adverse Events and Serious Adverse Events

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

8.2.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and is described in Section 11.14, with the exception of CRS, which will be graded using the criteria referenced in the publication by Lee et al (2014) (see Section 11.13) and TLS, which will be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al (2008) (see Section 11.14).

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(s)/study treatment/protocol-required therapies through the safety follow-up visit (30 [+3] days after the last dose of investigational product/study treatment/protocol-required therapies) are reported using the Event**s** CRF.

8.2.4.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed

consent through the **LTFU visit or End of Study Visit (whichever occurs later)** are reported using the Event**s** CRF.

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

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

8.2.4.1.3 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period **(as defined in Section 8.2.4.1.2)** or after end of study. However, these serious adverse events **should** be reported to Amgen **(regardless of causality) if the investigator becomes aware of them**. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

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

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

8.2.4.1.4 Reporting a Safety Endpoint as a Study Endpoint

Safety endpoints that are study endpoints are reported on the Event**s** CRF. All endpoints that also meet the criteria of serious adverse event must also be transmitted to safety within 24 hours of the investigator's knowledge of the event (refer to Section 11.4).

8.2.4.2 Method of Detecting Adverse Events and Serious Adverse Events

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

8.2.4.3 Follow-up of Adverse Events and Serious Adverse Events

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

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following 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**s** CRF.

8.2.4.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators. Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.2.4.5 Safety Monitoring Plan

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

8.2.4.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects will be collected after the start of study treatment and until 75 days after the last dose of AMG 910 or in a male subject's female partner through 5 months after the last dose of AMG 910.

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

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

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

8.2.5 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 1-1) 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**s** CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 1-1).

8.2.5.1 Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 48 hours of initiation of investigational product for all females of childbearing potential (see Section 11.5 for details).

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional pregnancy testing (urine or serum) should be performed within 48 hours of start of each following cycle during treatment with protocol-required therapies or at monthly intervals thereafter until 75 days after the last dose of protocol-required therapies.
Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

8.2.6 Pharmacokinetic Assessments

All subjects enrolled will have **PK** samples assessed.
Blood samples of approximately 2.5 mL will be collected for measurement of serum concentrations of AMG 910 as specified in the Schedule of Activities (Table 1-1). A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. 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.
PK samples should be collected at the exact nominal time point as noted. If unable to collect a PK sample at the specified nominal time point collect it as close as possible to the nominal time point and record the actual collection time. PK samples not collected at the exact nominal time point will not be considered protocol deviations

8.2.7 Pharmacodynamic Assessments

Venous blood samples will be collected for measurement of pharmacodynamic biomarkers at time points specified in the Schedule of Activities (Table 1-1).

8.2.8 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of gastric and gastroesophageal adenocarcinoma and/or to identify subjects who may have positive or negative response to AMG 910. Pharmacogenetic samples are collected for this part of

the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

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

8.2.10 Biomarkers

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

8.2.10.1 Biomarker Assessment to Determine Eligibility

In order to determine eligibility, expression of CLDN18 in tumor tissue will be determined.

Tumor Tissue

For a subject with unknown CLDN18.2 expression status or with prior CLDN18.2 targeting therapy to be eligible for study participation, tumor tissue is required prior to enrollment to establish CLDN18 positivity. Tumor sample(s) need(s) to be collected after informed consent is obtained, but prior to enrollment. **Archival tissue samples**

may be used for CLDN18.2 testing if available. If fresh tissue samples need to be collected, these samples should be obtained as part of patient standard of care or from endoscopic procedures, following local standard of care procedures that are not expected to present any additional significant risk to the health, safety, and welfare of the subject. Screening for CLDN18 will be conducted using either an approved or an investigational in vitro diagnostic (IVD) at a central laboratory as described in Section 11.2. Investigational devices will follow regional regulatory requirements. Timing of sample collection is described in the Schedule of Activities (Table 1-1).
Subjects previously tested positive for tumor expression of CLDN18 as participants of the Amgen study 20180293 **or Amgen study 20180290** are considered CLDN18 positive for screening purposes of the present study as long as no other CLDN18.2-targeting agent has been received in the interim.
The assay uses an immunohistochemistry-based detection of CLDN18. The assay is an investigational IVD[±] that will be used to prospectively inform subject selection for subjects with CLDN18-positive tumors for the enrollment phase of this study.
[±]The IVD described is CE marked to detect the biomarker in the EU.

8.2.10.2 Optional Tumor Biopsies

[redacted] The timepoint of this biopsy may be changed for all future cohorts based on emerging PK, pharmacodynamic and response data. In case a fresh biopsy is not required for screening purposes and archival tissue from a biopsy after the last therapy for gastric cancer is not available, an additional optional biopsy should be obtained if feasible during the screening period. Archival tissue samples should be collected and analyzed in addition where feasible. The comparison of the pre-treatment and the on-treatment tumor samples will allow for assessment of biomarkers on tumor cells and infiltrating T cells.
If subjects undergo a diagnostic or invasive intervention or surgery during the trial as per the investigator's discretion, subjects may consent to donate a portion of their tumor and/or associated tissues (eg, malignant effusion) to this study. The corresponding pathology report must be submitted for any biopsy provided for the study.
Eligible subjects who provide consent for a tumor biopsy must have tumor tissue that is accessible by endoscopic biopsy or by core biopsy using minimally invasive procedures.
[redacted]

[redacted]

8.2.10.3.1 Biomarker Development/Future Research

Biomarker Development**/Future Research** refers to using samples collected for Biomarker Discovery research.

In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the

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

If consent is provided by subjects, biomarker discovery samples collected at the time points specified in the Schedule of Activities will be retained for future biomarker development as described in Appendix 6 (Section 11.6). No additional samples will be collected for biomarker development/future research.

Amgen or another third-party manufacturer may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 910 to investigate and further understand gastric cancer.

9. Statistical Considerations

9.1 Statistical Hypotheses

AMG 910 will demonstrate acceptable safety and tolerability in subjects with gastric or GEJ cancer at 1 or more dose levels with at least 1 dose level showing evidence of anti-tumor activity.

9.2 Sample Size Determination

It is anticipated that approximately 70 subjects will be enrolled in this study. Up to 34 subjects will be enrolled in the dose-exploration cohorts and up to 36 additional subjects will be enrolled in the dose-expansion cohort.

The sample size in the dose-escalation phase is based on practical consideration and is consistent with conventional oncology studies with the objective to estimate the MTD. With 3 subjects in a cohort, there is a 27% to 70% probability of observing at least 1 DLT if the true DLT rate is 10% to 33% and with 4 subjects in a cohort, there is a 34% to 80% probability.

In the dose-expansion cohort, a subject number of 36 will provide an 84% probability of observing at least 1 adverse event with 5% incidence rate. An exact 95% binomial CI will be provided for overall response rate. With the 36 subjects and 19% overall response rate, the expected 95% CI would be 8% to 36%. Under certain circumstances, the sample size in dose expansion will be smaller due to early stopping; see Section 9.4.1.1 for details.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 910.

The analysis of DLT will be conducted on the DLT Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 910 with an evaluable DLT endpoint. See Section 6.2.1.1.2 for definition of DLT evaluable.

The analysis of objective response will be conducted on the RECIST and iRECIST Evaluable Analysis set defined as all subjects that are enrolled and receive at least 1 dose of AMG 910 with at least 1 tumor lesion that is measurable in contrast-enhanced computed tomography (CT) as defined by RECIST 1.1.

9.3.2 Covariates

If the number of responders is sufficient (eg, 10 or more) then the relationship of covariates to efficacy endpoints will be explored.

9.3.3 Subgroups

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

9.3.4 Handling of Missing and Incomplete Data

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

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 4.4.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. Based on accumulating toxicity information, BLRM will be used to make dosing recommendations. In DLRMs, Amgen,

in consultation with the site investigators, will review the BLRM recommended dose level and will review all available cumulative data by cohort prior to making dose escalation recommendations. As a sensitivity analysis, a 1-parameter Continual Reassessment Method model may be used to estimate the dose-toxicity relationship and to estimate the dose level closest to a 25% DLT rate in order to help make dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions.

During dose expansion, futility will be assessed after treating 15 and 25 subjects for at least 8 weeks of treatment. If the observed rate of responses is consistent with a lower than 15% response rate, enrollment may be terminated due to futility. As appropriate, enrollment to dose expansion may continue during the period of first 8 weeks follow up for response. For purposes of assessing futility, a response is defined as an objective response per RECIST 1.1. The guidelines for early termination due to futility are as follows:

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

If the true response rate is 15% then these termination guidelines result in a 69.4% probability of terminating dose expansion early with an expected sample size of 25 subjects. If the true response rate is 30% then there is a 90% probability of continuing enrollment to n = 36 total subjects.

During dose expansion, Amgen will conduct evaluations of the ongoing grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible early trial termination has been reached. If this threshold is met, enrollment to dose expansion will be halted pending review of safety data by the DLRT. After receiving the DLRT recommendation, Amgen will choose to take 1 of the following actions.

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

The stopping rules use a Bayesian approach proposed by Thall, Simon, and Estey (Thall, Simon, & Estey, 1995) to terminate the study if the posterior probability that the

grade 4 or higher treatment-related adverse event rate is greater than 20% is > 80%. The stopping boundaries assume a prior distribution of Beta (0.40, 1.60) are presented in Table 9-1 and the operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in Table 9-2. The operating characteristics in Table 9-2 provide the probability of stopping the trial early for given hypothetical true rate of grade 4 or higher treatment-related adverse events, whereas the stopping criteria in Table 9-1 are based on situations where the empirical evidence would result in a posterior probability of ≥ 80% that the true grade 4 or higher treatment-related adverse event rate is ≥ 20%. Also, if same CTCAE grade 4 stomach toxicity has been observed in ≥ 2 subjects, the risk/benefit of the study needs to be re-evaluated.

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

Number of subjects	Stop study if observing this many grade 4 or higher treatment-related adverse events
10	≥ 4
20	≥ 6
30	≥ 9
36	Dose Expansion Complete

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

True grade 4 or higher treatment-related adverse event rate	Probability of early stopping of dose expansion	Average dose expansion sample size
0.10	2.0%	35.6
0.15	9.7%	34.0
0.20	25.8%	30.9
0.25	47.7%	26.7
0.30	69.2%	22.2

9.4.1.2 Primary Analysis

The primary analysis for the safety endpoints, **PK** endpoints, and **OR** endpoints will occur when enrollment is complete**,** and each subject has had the opportunity to receive at least 6 cycles of treatment. The primary analysis for time to event endpoints (duration of response, time to progression, PFS, 6-month and 1-year PFS, OS, 1 and 2-year OS) will occur when enrollment is complete**,** and each subject has had the opportunity to be on study for at least 2 years**.**

9.4.1.3 Final Analysis

The final analysis will occur when target enrollment is complete for both phases and all subjects have ended the study. Primary and final analysis may be combined in case all subjects have ended study close to the time point of the primary analysis.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Unless otherwise specific, all described analyses will be conducted on the Safety Analysis Set. 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. Graphical summaries of the data may also be presented.

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

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	Listings of secondary efficacy endpoints will be produced for all subjects in the dose-escalation cohorts and the dose-expansion cohorts. The proportion of subjects with an objective response (per RECIST 1.1 and per iRECIST) and 95% CI will be tabulated by planned dose level using the RECIST Evaluable Analysis Set. For all subjects treated at the MTD and/or RP2D, Kaplan-Meier methods will be used to estimate the time to event curve, median time to event and percentiles with 95% CI for 1) duration of response (RECIST 1.1 and iRECIST) 2) time to progression 3) PFS 4) OS. For all subjects treated at the MTD and/or RP2D, Kaplan-Meier methods will be used to estimate 6-month and 1-year PFS, 1-year and 2-year OS with 95% CI.

Exploratory	Will be described in the statistical analysis plan finalized before database lock.

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the safety analysis set, which includes subjects that are enrolled and received AMG 910. The analysis of DLTs will be conducted on the DLT Analysis Set. Subject incidence of DLT will be tabulated by planned dose level. A table of DLT will be provided. The probability of a subject having a DLT by dose level will be estimated using a **2**-parameter BLRM model. The statistical analysis methods for other safety endpoints are described in Section 9.4.2.3.2-9.4.2.3.6.

9.4.2.3.2 Adverse Events

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

9.4.2.3.3 Laboratory Test Results

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

9.4.2.3.4 Vital Signs

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

9.4.2.3.5 Physical Measurements

Physical measurements will be reviewed for each subject.

9.4.2.3.6 Electrocardiogram

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

9.4.2.3.8 Exposure to Investigational Product

Details of AMG 910 administration will be listed for every subject.

9.4.2.3.9 Exposure to Concomitant Medication

All medication will be coded using the World Health Organization drug dictionary. A subject listing of all prior and concomitant medications will be presented.

9.4.2.4 Other Analyses

For AMG 910, **PK** parameters, including but not limited to C_{max}, minimum serum concentration (C_{min}), area under the concentration-time curve (AUC) over the dosing interval, accumulation following multiple dosing, and, if feasible, half-life ($t_{1/2}$), will be determined from the time concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. Based on the review of the data, analyses to describe the relationship between AMG 910 exposure and either pharmacodynamic effect and/or clinical outcome may also be performed.

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ADA	Anti-drug antibody
ALL	Acute lymphoblastic leukemia
aPTT	**activated partial thromboplastin time**
AUC	Area under the concentration-time curve
BiTE	Bi-specific T cell engager
BLRM	Bayesian logistic regression model
C0	Concentration at time 0
CBC	Complete blood count
CFR	U.S. Code of Federal Regulations
CLDN18.2	Claudin-18 isoform 2
Cmax	Maximum serum concentration
Cmin	Minimum serum concentration
c-MT	Mesenchymal epidermal transition
CNS	Central nervous system metastases
COVID-19	**SARS-CoV-2 Coronavirus Disease 2019**
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Computed tomography
ctDNA	Circulating tumor DNA
CTCAE	Common Terminology Criteria for Adverse Events
DES	Amgen data element standard
DILI	Drug induced liver injury
DLRM	Dose level review meeting
DLRT	Dose level review team
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DOR	Duration of response
DRT	Data review team
ECG	Electrocardiogram
Echo	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form

Abbreviation or Term	Definition/Explanation
EDC	Electronic data capture

Abbreviation or Term	Definition/Explanation
EGFR	Epidermal growth factor receptor
eIV	**Extended intravenous**
Electronic Source Data (eSource)	Source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
EOI	End of Infusion is considered as the end of the controlled rate post-infusion flush.
EOT	End of treatment
Exposure-Response Analysis	Mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic (PK) exposure (eg, population **PK** modeling) and response, which may include biomarkers, pharmacodynamic effects, efficacy and safety endpoints.
End of Follow-up	Defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	Defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	Defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), including any additional parts in the study (eg, long-term follow-up, additional antibody testing), as applicable
End of Treatment	Defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
Fc	Fragment crystallizable
GEJ	Gastroesophageal junction
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
HBV	**Hepatitis B virus**
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HLE	Half-life extended
HNSTD	Highest non-severely toxic dose
IB	**Investigator's Brochure**
IBG	Independent Biostatistics Group
ICF	Informed consent form

Abbreviation or Term	Definition/Explanation
ICH	International Conference on Harmonisation
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-10	Interleukin-10
INR	International normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IRT	Interactive response technology that is linked to a central computer in real time as an interface to collect and process information
IUD	Intrauterine device
IUS	Intrauterine hormonal-releasing system
IV	Intravenous
IVD	In vitro diagnostic
lu	Luciferase
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
MMR	**Mismatch repair**
MRI	Magnetic resonance imaging
MSI	**Microsatellite instability**
MSI-H	Microsatellite instability-high
MTD	Maximum tolerated dose
MUC17	**mucin-17**
NCT	National Clinical Trials
NSAID	Non-steroidal anti-inflammatory drug
OR	Objective response
OS	Overall survival
PB	Peripheral blood
PD	Disease progression
PD-L1	**programmed death-ligand 1**
PFS	Progression-free survival
PK	Pharmacokinetics

Abbreviation or Term	Definition/Explanation
PT	Prothrombin time
PTT	Partial thromboplastin time
PRE	Pre-dose
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAT	Safety assessment team
scFc	Single chain fragment crystallizable
SCR	Screening
SFU	Safety follow-up
SoA	**Schedule of Activities**
Source Data	Information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	Defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
SUSAR	Suspected unexpected serious adverse reaction
t1/2	Half-life
TBL	Total bilirubin
TIL	**tumor infiltrating lymphocytes**
TK	Toxicokinetic
TKI	Tyrosine kinase inhibitor
TLS	Tumor Lysis Syndrome
TMB	**Tumor mutation burden**
TMF	Trial master file
TNF	Tumor necrosis factor
ToGA	Trastuzumab for Gastric Cancer
ULN	Upper limit of normal
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 and Table 11-2 will be performed by the local laboratory and/or by the central laboratory.

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

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

Table 11-1. Local Laboratory Analyte Listing

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium	PTT **or a**PTT	Specific gravity	RBC	Serum or Urine Pregnancy
Potassium	PT **or** INR	pH	Nucleated RBC	Hep B surface antigen
Chloride	Fibrinogen	Blood	Hemoglobin	Hep C antibody
Bicarbonate	D-dimer	Protein	Hematocrit	HIV
Total protein		Glucose	MCV	Optional tumor markers as appropriate and in line with local standards
Albumin		Bilirubin	MCH	
Calcium		WBC	MCHC	
Adjusted calcium		RBC	RDW	
Magnesium		Epithelial cells	Reticulocytes	
Phosphorus		Bacteria	Platelets	
Glucose		Casts	WBC	
BUN or Urea		Crystals	Differential	
Creatinine			• Bands/stabs	
Uric acid			• Segmented neutrophils	
Total bilirubin			• Eosinophils	
Direct bilirubin			• Basophils	
ALP			• Lymphocytes	
LDH			• Monocytes	
AST (SGOT)			• Total neutrophils	
ALT (SGPT)				
Amylase				
Lipase				
CRP				
Ferritin				

ACTH = **a**drenocorticotropic hormone; **ALP = alkaline phosphatase; ALT = alanine aminotransferase;** ANA = **a**ntinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; ANC = absolute neutrophil count; **aPTT = activated partial thromboplastin time;** AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; GFR = glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; **PTT = partial thromboplastin time;** RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count**.**

[a] Creatinine clearance will be calculated using the MDRD formula

Table 11-2. Central Laboratory Analyte Listing

11.3 Appendix 3. Study Governance Considerations

Dose Level Review Team

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

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

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

All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, ECG, vital signs, and laboratory results will be reviewed. Data to be reviewed will be queried.

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

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

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

Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product. Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.
The investigator will be responsible for the following:

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

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 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 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 7.

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

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

If a potential subject is illiterate or visually impaired, 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 the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

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

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

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the

regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

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

Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4. When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be

submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.
The coordinating investigator, identified by Amgen, will be any or all of the following:

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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
The sponsor or designee is responsible for the data management of this study including quality checking of the data.
Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.
The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.
The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and,

upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

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

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

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

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

Source Documents

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

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

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

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for

inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

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

Study and Site Closure

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

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

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

Compensation

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

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

Definition of Adverse Event

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

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

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

Definition of Serious Adverse Event

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

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**s** case report form (CRF). • The investigator must assign the following adverse event attributes: o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); o Dates of onset and resolution (if resolved); o **Did the event start prior to first dose of investigational product, other protocol-required therapies;** o **Assessment of seriousness;** o Severity (or toxicity defined below); o Assessment of relatedness to investigational product (AMG 910), other protocol-required therapies**,** and/or study-mandated activity **and/or** procedure**s;** 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**s** 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**s** CRF page. • If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

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

The Common Terminology Criteria for Adverse Events, version 5.0 which is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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 11.13) 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 11.14).

Assessment of Causality

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

- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

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

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

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

event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Report Form

A **Study # 20180292** **AMG 910**	**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 (AMG 910) or an Amgen device used to administer the IP? AMG 910 No✓ Yes✓	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria:			
	01 Fatal	03 Required/prolonged hospitalization	05 Congenital anomaly / birth defect
	02 Immediately life-threatening	04 Persistent or significant disability /incapacity	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 910	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Report Form

A Study # 20180292 AMG 910	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

	Site Number	Subject ID Number	

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Report Form

A **Study # 20180292** **AMG 910**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

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

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

Study-specific contraception requirements for male and female of childbearing potential are outlined in Section 5.2.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 75 days for females and 5 months for males 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 5 months after the last dose of protocol-required therapies

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

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

Unacceptable Methods of Birth Control for Male and Female Subjects

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

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through an additional 75 days after discontinuation of the study drug.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed consent 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 an additional 75 days after discontinuation of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.2. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 5 months after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through an additional 75 days after discontinuation of the study drug.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 216.
- 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 an additional 75 days after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20180292

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
AMG 910				mm____/dd____/yyyy____

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/yyyy_____

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

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

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

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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

Figure 11-2. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20180292

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
AMG 910				mm____/dd____/yyyy____

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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

11.6 Appendix 6. Sample Storage and Destruction

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

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

[redacted] Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining sample types (eg, blood, tumor) samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no

longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

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

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

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

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

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

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

If investigational product(s) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 11-3. 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 AMG 910 is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-3) 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**s** CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 11.4.

Additional Clinical Assessments and Observation

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

Assessments that are to be performed during this period include:

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

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

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

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

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

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

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

11.8 Appendix 8. Protocol-specific Anticipated Serious Adverse Events

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

Anticipated Serious Adverse Events for Study 20180292

Weight decreased
Decreased appetite
Fatigue
Anaemia
Gastric obstruction
Helicobacter infection
Pernicious anaemia
Barrett's oesophagus
Dyspepsia
Gastrooesophageal reflux disease
Nausea
Vomiting
Abdominal pain
Gastritis
Gastric hemorrhage
Gastric perforation

For metastatic site-related adverse events, events will be evaluated for ASAEs on a case by case basis (eg, intestinal obstruction for intestinal metastatic disease state, increase in transaminase for liver metastatic disease present at baseline).

11.9 Appendix 9. Operating Characteristic for 2-parameter BLRM Design

The operating characteristics of the **2**-parameter Bayesian logistic regression model (BLRM) design were evaluated via simulation using EAST software version 6.4.1. A bi-variate normal prior distribution (parameters "a" and "b") is used for the BLRM model. The prior distribution is specified such that probability of dose-limiting toxicity (DLT) is 0.05 for the starting dose (6.5 µg) and 0.3 for the reference dose (3500 µg), where the probability that the true DLT rate is ≤ 0.40 at the lowest planned dose is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose is 0.05. In particular, the parameters of the bi-variate normal prior are as follows: the mean natural log (ln) of "a" ln(a) = -0.847, standard deviation (SD) of "a" SD(a) = 1.275, mean ln(b) = -1.098, SD(b) = 1.981 and correlation = 0.

The planned cohort size for the initial 2 cohorts is n=1 subject and the cohort size for subsequent cohorts is fixed to 3 or 4 subjects; based on observed toxicity in the initial 2 cohorts, the cohort size for any or all of the initial 2 cohorts may be increased to n = 3 to 4 subjects. Planned dose levels are 6.5, 20, 65, 200, 400, 650, 1000, 1500, 2300 and 3500 µg. After simulated enrollment of the initial cohort at the initial dose level, simulations selected the subsequent dose levels based on the following rules:

- After each cohort, the next dose was the 1 with the highest probability of the target toxicity probability interval (TPI), but with a less than 0.40 probability of an excessive or unacceptable TPI.
- Skipping a planned dose level was not allowed.

Dose exploration was stopped when either of the following occurred:

- The model recommended a dose level where at least 6 subjects had already received treatment at this recommended level.
- A maximum number of 34 subjects were treated.

Operating characteristics are described below.

Operating characteristics

The design was evaluated for 4 possible dose-response scenarios: "Low", "Mid", and "High" maximum tolerated dose (MTD) and an "Extreme" scenario where every planned dose level was excessively toxic. Table 11-4 shows the dose level and true probability of dose-limiting toxicity (DLT) for each scenario used in the simulated studies. Since the timing of initiation of the multiple subject cohorts impacts the design operating characteristics, the operating characteristics were calculated separately for each possible timing for starting the multiple subject cohorts: at cohort 1, cohort 2 and at

cohort 3. Overall operating characteristics are reported after weighting the 3 timing-specific operating characteristics by the probability that a specific cohort is the initial multiple subject cohort. Table 11-5 shows the dose level and true probability of a DLT or a grade 2 related adverse event for each scenario used in the simulated studies. Using the toxicity rates described in Table 11-5, the probability by cohort for initiating the multiple subject cohorts are shown in Table 11-6. Table 11-7 reports the operating characteristics from 1000 simulated studies estimating the MTD when the target TPI is (0.20, 0.33]. The rate of MTD selected and the average number of subjects assigned to each dose level are presented in Table 11-8.

Table 11-4. True Probability of DLT by Scenario

Dose level (µg)	6.5	20	65	200	400	650	1000	1500	2300	3500
MTD scenario										
High	0.01	0.04	0.08	0.10	0.12	0.15	0.20	0.30	0.40	0.50
Mid	0.08	0.10	0.12	0.15	0.20	0.30	0.40	0.50	0.60	0.70
Low	0.12	0.15	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90
Extreme	0.35	0.40	0.45	0.55	0.60	0.65	0.70	0.75	0.80	0.95

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

Table 11-5. True Probability of DLT or Grade 2 Related Adverse Event by Scenario

Dose level (µg)	6.5	20	65	200	400	650	1000	1500	2300	3500
MTD scenario										
High	0.06	0.09	0.13	0.15	0.17	0.25	0.30	0.40	0.50	0.60
Mid	0.13	0.15	0.17	0.25	0.30	0.40	0.50	0.60	0.70	0.80
Low	0.17	0.25	0.30	0.40	0.50	0.60	0.70	0.80	0.90	0.95
Extreme	0.45	0.50	0.55	0.65	0.70	0.75	0.80	0.85	0.90	0.99

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

Table 11-6. Probability by Planned Dose Level for Initiating Multiple Subject Cohorts by Scenario

Dose level (μg) for initiating multiple subject cohorts	6.5	20	65
MTD scenario			
High	0.06	0.08	0.86
Mid	0.13	0.13	0.74
Low	0.17	0.21	0.62
Extreme	0.45	0.27	0.27

Table 11-7. Operating Characteristics by Scenario

MTD scenario	**High**		**Mid**		**Low**		**Extreme**	
Number of subjects per cohort	4	3	4	3	4	3	4	3
Average number of subjects on study	30.1	25.2	26.2	20.8	19.5	16.1	9.3	8.1
Average number of DLTs on study	5.2	4.8	5.9	5.0	5.4	4.7	3.9	3.4
Percentage of studies by actual DLT probability of estimated MTD:								
MTD below lowest planned dose	3.1	1.7	6.4	6.2	19.8	16.7	79.9	68.8
DLT probability at estimated MTD								
$< 10\%$	1.3	2.1	0.1	0.2	0	0	0	0
$\geq 10\%$ and $< 20\%$	17.6	18.5	17.3	19.4	5.2	5.7	0	0
$\geq 20\%$ and $< 33\%$	56.1	54	51.4	46.5	52.9	49.5	0	0
$\geq 33\%$	18.3	19	24.7	27.7	22	28.3	19.1	30.1
$\geq 15\%$ and $\leq 33\%$	66.2	64.6	63.4	58.7	57.3	53.7	0	0

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

Table 11-8. The Rate of MTD Selected and the Number of Subjects Assigned at Each Dose Level by Scenario

MTD scenario	High		Mid		Low		Extreme	
Number of subjects per cohort	4	3	4	3	4	3	4	3
Rate of MTD selected at each dose level (%):								
Below lowest dose	3.1	1.7	6.4	6.2	19.8	16.7	79.9	68.8
6.5 µg	0	0	0.1	0.2	0.8	1.5	4.7	8.4
20 µg	0	0.1	0.6	1.1	4.4	4.2	6.7	8.6
65 µg	1.3	2	4.7	6.1	22.4	21.6	6	9.5
200 µg	2.8	3.4	12	12.2	30.5	27.9	1.5	3.1
400 µg	4.7	4.5	22.8	19.7	16.5	20	0.2	0.4
650 µg	10.1	10.6	28.6	26.8	4.8	6.9	0	0.1
1000 µg	23.7	22.3	18.6	18.7	0.6	1.3	0	0
1500 µg	32.4	31.7	5.6	8	0.1	0.1	0	0
2300 µg	18.3	19	0.5	1	0	0	0	0
3500 µg	3.7	4.7	0	0.1	0	0	0	0
Average number of subjects at each dose level								
6.5 µg	0.2	0.2	0.7	0.5	1.2	1	2.8	2.2
20 µg	0.7	0.6	1.3	1.1	2.5	1.9	2.9	2.4
65 µg	4.4	3.4	4.7	3.6	5.5	4.2	2.6	2.3
200 µg	4.5	3.4	5	3.6	5.1	3.9	0.8	0.9
400 µg	4.5	3.4	5.2	3.8	3.4	2.9	0.2	0.2
650 µg	4.7	3.6	4.8	3.7	1.4	1.6	0	0.1
1000 µg	4.8	3.8	3.2	2.8	0.4	0.5	0	0
1500 µg	4.1	3.7	1.1	1.3	0	0.1	0	0
2300 µg	1.9	2.4	0.2	0.4	0	0	0	0
3500 µg	0.3	0.7	0	0	0	0	0	0

MTD = maximum tolerated dose

11.10 Appendix 10. 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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group.
Source: Oken, et al., 1982

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

Quick Reference

This study utilizes RECIST 1.1 criteria. Details of implementation of the criteria will be provided in the site reader web-based training.

Definitions

- **Measurable Lesions**
  - Measurable Tumor Lesions – Non-nodal lesions with clear borders that can be accurately measured in at least 1 dimension with longest diameter ≥ 10 mm in CT/MRI scan with slice thickness no greater than 5 mm. When slice thickness is greater than 5 mm, the minimum size of measurable lesion should be twice the slice thickness.
  - Nodal Lesions - Lymph nodes are to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI (scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
    - Nodal size is normally reported as 2 dimensions in the axial plane. The smaller of these measures is the short axis (perpendicular to the longest axis).
  - Irradiated Lesions - Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not measurable unless there has been demonstrated progression in the lesion prior to enrollment.
- **Non-measurable Lesions**
  - All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm but to < 15 mm short axis with CT scan slice thickness no greater than 5 mm) are considered non-measurable and characterized as non-target lesions.
  - Other examples of non-measurable lesions include:
    - Lesions with prior local treatment: tumor lesions situated in a previously irradiated area, or an area subject to other loco-regional therapy, should not be considered measurable unless there has been demonstrated progression in the lesion.
    - Biopsied lesions
    - Categorially, clusters of small lesions, bone lesions, inflammatory breast disease, and leptomeningeal disease are non-measurable.

Methods of Measurement

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

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

- **Target Lesions** - All measurable lesions up to a maximum of two (2) lesions per organ and five (5) lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
    - Target lesions should be selected on the basis of their size (lesions with the longest diameter) and suitability for accurate repeated measurements.

Pathologic lymph nodes (with short axis ≥ 15 mm) may be identified as target lesions.

All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions.

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

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

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

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

iRECIST Disease Categories

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

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

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

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

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

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

iRECIST Calculations

The iRECIST criteria requires the calculation of target lesion sum of measures (SOM) and new target lesion sum of measures (SOM). These are 2 distinct sums:

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

Tumor Response Assessment

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

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

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

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

When iUPD is followed by tumor shrinkage, this is referred to as “resetting the bar” and is 1 of the most important concepts of iRECIST. A subject cannot be assessed as iCPD at the time point immediately after “resetting the bar.” Disease must again qualify for iUPD, then worsen to be assessed as iCPD.

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

Target Lesion Assessments

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

Table 11-9. iRECIST Target Lesion Assessments

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

Non-Target Lesion Assessments

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

Table 11-10. iRECIST Non-target Assessments

iRECIST Non-Target Lesion Assessments	Requirements
Immune Complete response (iCR)	Requires disappearance of all non-nodal non-target lesions and normalization of pathological non-target lymph nodes to <10 mm in short axis
Immune Unconfirmed Progressive Disease (iUPD)	Requires unequivocal progression of non-target lesions
Non-iCPD/non-iUPD	Requires persistence of 1 or more non-target lesions and not meeting the non-target lesion requirements for iCR or iPD
Immune Confirmed Progressive Disease (iCPD)	Requires worsening of non-target lesions in comparison to an immediately prior non-target lesion assessment of iUPD.

New Lesions

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

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

Overall response

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

Table 11-11. iRECIST Overall Response

iRECIST Target Lesion Assessments	Requirements

Immune Complete Response (iCR)	• Can only be assessed after the initial iRECIST iUPD time point (ie, the time point of RECIST 1.1 PD)
	• Requires all of the following:
	  • Disappearance of all non-nodal target lesions and normalization of pathological target lymph nodes to <10 mm in short axis – if any were present
	  • Disappearance of all non-nodal non-target lesions and normalization of pathological non-target lymph nodes to < 10 mm in short axis - if any were present
	  • No new lesions can appear for the first time or persist. Any previously identified new lesions must have disappeared.

Immune Partial Response (iPR)	• Can only be assessed after the initial iRECIST iUPD time point (ie, the time point of RECIST 1.1 PD)
	• Requires all of the following:
	  • ≥ 30% decrease in sum of measures of target lesions with reference to the baseline target lesion sum
	  ▪ The reference time point is the subject's original baseline time point acquired prior to drug initiation
	  • Non-target persistence without worsening or non-target complete resolution
	  • No new lesions can appear for the first time. No worsening of new lesions. Persistent new lesions can be present if unchanged.

Immune Unconfirmed Progressive Disease (iUPD)	• Always assessed at the time point of RECIST 1.1 PD (ie, the initial iRECIST iUPD time point), can also be assessed after RECIST 1.1 PD
	• Requires any of the following:
	  • ≥ 20% and a ≥ 5 mm increase in the sum of measures of target lesions, with reference to nadir time point (ie, the time point with the smallest target lesion sum on study)
	  ▪ The reference time point is the time point with the smallest target sum since (and including) the original baseline
	  • Unequivocal progression of non-target lesions
	  • First appearance of new lesions

Immune Stable Disease (iSD)	• Can only be assessed after the initial iRECIST iUPD time point (ie, the time point of RECIST 1.1 PD) • Is assessed when the requirements for iCR or iPR are not met, in the absence of iUPD
Immune Confirmed Progressive Disease (iCPD)	See **Table 11-12**

Table 11-12. iCPD Requirements Summary

Immune Confirmed Progressive Disease (iCPD) Requirements	
An overall response of iCPD can only be assessed immediately after a time point with overall response of iUPD[1]	
Cause of iUPD	**iCPD Requirements**
Target Lesion Progression	Additional worsening of target lesions as evidence by an increase of ≥ 5mm in the target lesion SOM
Non-Target Lesion Progression	Any worsening in non-target lesions
New Target Lesions	Additional worsening of new target lesions as evidenced by an increase of ≥ 5mm in the new target lesion SOM, or additional new target lesions
New Non-Target Lesions	Any worsening in non-target lesion lesions or additional non-target new lesions
Any cause	New RECIST 1.1-assigned progression in another lesion category (ie, target or non-target lesions reach the definition of iUPD for the first time per Table 1 or Table 2, or there are new lesions for the first time)

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

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

Best Overall Response

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

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

Special cases

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

Methods of Assessment and Image Acquisition Specifications

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

11.13 Appendix 13. Specific Guidance for Cytokine Release Syndrome

Cytokine release syndrome (CRS) 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 910. CRS may be life threatening or fatal. Infusion reactions may be clinically indistinguishable from manifestations of CRS. Throughout the treatment with AMG 910, 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 (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 interruptions/delay/withholding and dose modifications in Section 6.2.2**, Table 6-3 and Table 6-4.**

For grade 3 and 4 CRS, please also see Section 6.2.1.3 for DLT considerations.

11.14 Appendix 14. 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 11-13) and clinical TLS (see Table 11-14) including grading.

Based on the Cairo and Bishop system, laboratory TLS is defined as any 2 or more abnormal serum values present within 3 days before or 7 days after initiation of treatment in the setting of adequate hydration (with or without alkalization) and use of a hypouricemic agent (Table 11-14).

Table 11-13. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

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 mol/L for adults	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

Note: Two or more laboratory changes within 3 days before or 7 days after cytotoxic therapy will constitute laboratory tumor lysis syndrome.

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 11-13). The grade of clinical TLS is defined by the maximal grade of the clinical manifestations as detailed in Table 11-14.

Table 11-14. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

Grade	Creatinine[a, b]	Cardiac arrhythmia[a]	Seizure[a]
0	≤ 1.5 x ULN	None	None
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

11.15 Appendix 15. Protocol Amendment 2 Schedule of Activities (SoA) for Cohort 1

Table 1-1. Schedule of Activities

	SCR[a]	Treatment Cycle 1																																							
Week		1											2										3										4									
Cycle Day		1				2	3				4	5	8				9	10				11	15				16	17				18	22				23	24				25
Hour (relative to EOI[b])		PRE	0	EOI	4	24	PRE	0	EOI	4	24	48	PRE	0	EOI	4	24	PRE	0	EOI	4	24	PRE	0	EOI	4	24	PRE	0	EOI	4	24	PRE	0	EOI	4	24	PRE	0	EOI	4	24
GENERAL AND SAFETY ASSESSMENTS																																										
Informed consent	X																																									
Clinical evaluation[c]	X	X				X	X				X	X	X				X	X				X	X				X	X				X	X				X	X				X
Vital signs, pulse oximetry	X	X		X[d]			X		X[d]			X	X		X[d]			X		X[d]			X		X[d]			X		X[d]			X		X[d]			X		X[d]		
12-lead ECG[e] triplicate	X	X		X			X		X				X		X			X		X			X		X										X					X		
Adverse events review		Continually throughout study																																								
Serious adverse events review		Continually throughout study																																								
Prior/concomitant medication		Continually throughout study																																								
LOCAL LABORATORY ASSESSMENTS																																										
Pregnancy test[f]	X	X																																								
HIV, Hepatitis B and C screening	X																																									
CBC with differential	X	X			X	X	X			X	X		X			X	X	X			X	X	X				X	X				X	X				X	X				X
Coagulation	X	X			X	X	X			X	X		X			X	X	X			X	X	X				X	X				X	X				X	X				X
Chemistry panel	X	X			X	X	X			X	X		X			X	X	X			X	X	X				X	X				X	X				X	X				X
Urinalysis	X						X																	X																		
Gastroscopy[g]	X[g]																		X[g]																							
CENTRAL LABORATORY ASSESSMENTS																																										
[redacted]																																										
STUDY TREATMENT AND OTHER ASSESSMENTS / PROCEDURES																																										
Imaging		See Table 1-3 - imaging assessments																																								
AMG 910 short term IV infusion			X					X						X					X					X					X					X					X			
Hospital stay		From Day 1 until 48 hours after EOI on Day 3											Until 48 hours after EOI on Day 8 and Until 24 hours after EOI on Day 10										Until 24 hours after EOI on Day 15					Until 24 hours after EOI on Day 17					Until 24 hours after EOI on Day 22					Until 24 hours after EOI on Day 24				

Page 1 of 5

Abbreviations and footnotes defined on last page of table

Table 1-1. Schedule of Activities

	Treatment Cycle 2[l]																													
Week	1								2								3								4					
Cycle Day	1				3				8				10				15				17				22				24			
Hour (relative to EOI[b])	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4
GENERAL AND SAFETY ASSESSMENTS																																
Clinical evaluation[c]	X			X	X			X	X			X	X			X	X			X	X			X	X			X	X			X
Vital signs, pulse oximetry	X		X[d]		X		X[d]		X		X[d]		X		X[d]		X		X[d]		X		X[d]		X		X[d]		X		X[d]	
12-lead ECG[e]	X																															
Adverse events review	Continually throughout study																															
Serious adverse events review	Continually throughout study																															
Prior/concomitant medication	Continually throughout study																															
LOCAL LABORATORY ASSESSMENTS																																
Pregnancy test[f]	X																															
CBC with differential	X			X	X			X	X			X	X			X	X			X	X			X	X			X	X			X
Coagulation	X			X	X			X	X			X	X			X	X			X	X			X	X			X	X			X
Chemistry panel	X			X	X			X	X			X	X			X	X			X	X			X	X			X	X			X
Urinalysis					X													X														
Gastroscopy[g]														X[g]																		
CENTRAL LABORATORY ASSESSMENTS																																
[redacted]																																
STUDY TREATMENT AND OTHER ASSESSMENTS / PROCEDURES																																
Imaging	See Table 1-3 - imaging assessments																															
AMG 910 short term IV infusion		X				X				X				X				X				X				X				X		
Observation	Until 4 hours after EOI on Day 1				Until 4 hours after EOI on Day 3				Until 4 hours after EOI on Day 8				Until 4 hours after EOI on Day 10				Until 4 hours after EOI on Day 15				Until 4 hours after EOI on Day 17				Until 4 hours after EOI on Day 22				Until 4 hours after EOI on Day 24			

Page 2 of 5

Abbreviations and footnotes defined on last page of table

Table 1-1. Schedule of Activities

	Treatment Cycle 3																
Week	1					2				3				4			
Cycle Day	1				2	8				15				22			
Hour (relative to EOI[b])	PRE	0	EOI	4	24	PRE	0	EOI	8	PRE	0	EOI	4	PRE	0	EOI	4
GENERAL AND SAFETY ASSESSMENTS																	
Clinical evaluation[c]	X			X	X	X			X	X			X	X			X
Vital signs, pulse oximetry	X		X[d]			X		X[d]		X			X	X			X
12-lead ECG[e]	X																
Adverse events review	Continually throughout study																
Serious adverse events review	Continually throughout study																
Prior/concomitant medication	Continually throughout study																
LOCAL LABORATORY ASSESSMENTS																	
Pregnancy test[f]	X																
CBC with differential	X			X		X			X	X			X	X			X
Coagulation	X			X		X			X	X			X	X			X
Chemistry panel	X			X		X			X	X			X	X			X
Urinalysis	X									X							
CENTRAL LABORATORY ASSESSMENTS																	
[redacted]																	
STUDY TREATMENT AND OTHER ASSESSMENTS / PROCEDURES																	
Imaging	See Table 1-3 - imaging assessments																
AMG 910 short term IV infusion		X					X				X				X		
Hospital Stay (Day 1 only)	Until 24 hours after EOI on Day 1																
Observation						Until 8 hours after EOI on Day 8				Until 4 hours after EOI on Day 15				Until 4 hours after EOI on Day 22			

Page 3 of 5

Abbreviations and footnotes defined on last page of table

Table 1-1. Schedule of Activities

	Treatment Cycles 4 through 6[l]																EOT[j]	SFU	LTFU
Week	1				2				3				4						
Cycle Day	1				8				15				22				28		
Hour (relative to EOI[b])	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4	PRE	0	EOI	4			
GENERAL AND SAFETY ASSESSMENTS																			
Clinical evaluation[c]	X			X	X			X	X			X	X			X	X	X	
Vital signs, pulse oximetry	**X**			**X**	**X**			**X**	**X**			**X**	**X**			**X**	**X**	**X**	
12-lead ECG[e]	X																		
Adverse events review	Continually throughout study																		
Serious adverse events review	Continually throughout study																		
Prior/concomitant medication	Continually throughout study																		
Survival Status and/or subsequent cancer therapy																			X
LOCAL LABORATORY ASSESSMENTS[n]																			
Pregnancy test[f]	X																	**X**	
CBC with differential	X			X	X			X	X			X	X			X	X	X	
Coagulation	X			X	X			X	X			X	X			X	X	X	
Chemistry panel	X			X	X			X	X			X	X			X	X	X	
Urinalysis	X								X										
CENTRAL LABORATORY ASSESSMENTS																			
[redacted]																			
STUDY TREATMENT AND OTHER ASSESSMENTS / PROCEDURES																			
Imaging	See Table 1-3 - imaging assessments																		
AMG 910 short term IV infusion		X				X				X				X					
Observation	**Until 4 hours after EOI on Day 1**				Until 4 hours after EOI on Day 8				**Until 4 hours after EOI on Day 15**				**Until 4 hours after EOI on Day 22**						

Abbreviations and footnotes defined on last page of table

Table 1-1. Schedule of Activities

	Treatment-free Intervals after Cycles 2 and 4 (2 weeks)[m]	
Week	1	2
Day[k] (out of 14-day treatment-free interval)	1	8
GENERAL AND SAFETY ASSESSMENTS		
Clinical evaluation[c]	X	X
Vital signs, pulse oximetry	X	X
Adverse events review	Continually throughout study	
Serious adverse events review	Continually throughout study	
Prior/concomitant medication	Continually throughout study	
LOCAL LABORATORY ASSESSMENTS		
CBC with differential	X	X
Coagulation	X	X
Chemistry panel	X	X
Urinalysis	X	
OTHER ASSESSMENTS / PROCEDURES		
Imaging	See Table 1-3 - imaging assessments	

AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; EOI = end of infusion; EOT = end of treatment; IV = intravenous; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; Pre = pre-infusion; SAE = serious adverse event; SCR = screening; SFU = safety follow-up; ctDNA = circulating tumor DNA; PB = peripheral blood

[a] All screening procedures should be performed within 21 days prior to cycle 1 day 1 dosing **if not stated differently in Section 8.1.1**.

[b] End of Infusion (EOI) is considered as the end of the controlled rate post-infusion flush.

[c] Clinical evaluation including physical exam, ECOG, weight, and neurological examination (as described in Section 8.2.1.5). Performed at Screening only: demographics, medical history, and height.

[d] Refer to Section 8.2.3.1 **and Section 8.2.3.2** for additional vital sign **and pulse oximetry** collection time points.

[e] Triplicate ECGs to be collected at Screening and in Cycle 1 only. Single ECGs will be collected per time point for Cycle 2 and beyond. Refer to Section 8.2.3.3.

[f] Pregnancy testing is required for all female subjects **of childbearing potential**. Serum pregnancy test at Screening and within 48 hours prior to first dose of AMG 910. Beginning with Cycle 2 and beyond, **within 48 hours of start of each following cycle during treatment with protocol-required therapies or at monthly intervals thereafter until 75 days after the last dose of protocol-required therapies.**

[redacted]

[j] EOT visit will take place on Cycle 6 Day 28 (± 2 days).

[k] Visits during the 14-day treatment-free intervals will be completed on the first day of each week (± 2 days).

[l] After Cycles 2 and 4, refer to page 3 of Table 1-1 for assessments performed during the two-week treatment-free intervals.

[m] There will be planned treatment-free intervals of 2 weeks after cycles 2 and 4. This may be extended up to 3 weeks for reasons described in Section 4.1. If there is a 3rd week of observation, the same assessments are to be performed on Day 15 as on Days 1 and 8 of the treatment-free interval.

[n] **Laboratory assessments that were done within 24 hours prior to infusion do not need to be repeated.**

Table 1-2. Schedule of Pharmacokinetic Samples[a]

	Pre-infusion	End of infusion (EOI[b])	Hours after end of infusion			
			2	4	24	48
Cycle 1 (day 1)	X	X	X	X	X	
Cycle 1 (day 3)	X	X		X	X	X
Cycle 1 (days 8 and 10)	X	X		X	X	
Cycle 1 (days 15, 17, and 22)	X	X				
Cycle 1 (day 24)	X	X	X	X	X	
Cycle 2 (days 1, 3, 8, 10, 15, 17, and 22)	X	X				
Cycle 2 (day 24)	X	X	X	X		
Cycle 3 (day 1)	X	X	X	X	X	
Cycle 3 (days 8, 15, and 22)	X	X				
Cycles 4, 5, and 6 (day 1)	X	X				

[a] PK samples should be collected at the exact nominal time point as noted. If unable to collect a PK sample at the specified nominal time point collect it as close as possible to the nominal time point and record the actual collection time. PK samples **collected ± 15 minutes from planned** nominal time point will not be considered protocol deviations.
[b] End of Infusion (EOI) is considered as the end of the controlled rate post-infusion flush.

Table 1-3. Schedule of Imaging Assessments (Cycle Independent)

	SCR	Treatment Period	EOT	SFU	LTFU	Notes
MRI brain	X					All subjects must have MRI of the brain performed within 21 days prior to the first dose of AMG 910. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain can be performed at any time if clinically indicated per standard of care
Contrast enhanced CT and tumor burden[a] assessment[b]	X	• Every 6 weeks for first 12 weeks • Every 8 weeks thereafter	X	X	X[a]	Radiologic imaging (CT) is required at the EOT or SFU visit if the subject has not had radiologic imaging performed within 8 weeks of the visit.

CT = computed tomography; EOT = end of treatment; **ICF = Informed Consent Form;** LTFU = long-term follow-up; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors; iRECIST = immune Response Evaluation Criteria in Solid Tumors; SCR = screening; SFU = safety follow-up

[a] **Optional tumor marker collection in line with imaging and local standards.**

[b] For subjects who discontinued treatment for any reason other than confirmed disease progression, every effort should be made to perform radiographic imaging (CT) of the chest, abdomen, pelvis, and all other known sites of disease every 3 months until documentation of confirmed disease progression per RECIST 1.1 and iRECIST, clinical progression, start of new anticancer therapy, or up to 2 years after the first dose of AMG 910, whichever occurs first.

Notes: If CT and/or MRI is done prior to ICF signature results can be used if the subjects allows its use and assessments are done within 30 days of C1 day 1, as outlined in Section 8.1.1.

There is a tolerability window of ± 1 week for the imaging assessments.

Amendment 3

Protocol Title: A Global Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of the Half-life Extended Bispecific T-cell Engager AMG 910 in Subjects With Claudin 18.2-Positive Gastric and Gastroesophageal Junction Adenocarcinoma

Amgen Protocol Number 20180292

Amendment Date: 02 March 2021

Rationale:

This protocol is being amended to include the following updates:

- To adapt duration of extended intravenous (eIV) administration during cycle 1 week 1 within a range of 3 to 7 days.
- Following cycle 1 week 1, which will be eIV, dose administration will switch to once weekly dosing schedule starting cycle 1 day 8
- To update the planned target doses of AMG 910 as 6.5, 15, 30, 60, 150, 300, 600, 1000, and 2000 μg.
- To update the predicted pharmacokinetic (PK) profile for AMG 910 eIV Infusion from the planned doses.
- To update the inclusion criteria (102) to include the legal age within the country.
- To update the inclusion criteria (104) to include the standards and approvals within the country.
- To update the exclusion criteria (206) with respect to subjects with positive hepatitis B core antibody and/or hepatitis B surface antibody (HBsAb) accompanied by a negative Hepatitis B virus-DNA (HBV-DNA) can be enrolled into the study, but HBV-DNA needs to be monitored every 2 months.
- To update long-term follow-up (LTFU).
- To add a 48 hours column for day 8 to the Schedule of Activities (SoA) and also other assessment timepoint in cycle 1.
- To separate Table 6-3 (short-term IV) and Table 6-4 (new table added for eIV)
- Editorial changes (including typographical, grammatical, abbreviation, and formatting) have been made throughout the document.

Amendment 2

Protocol Title: A Global Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of the Half-life Extended Bispecific T-cell Engager AMG 910 in Subjects With Claudin 18.2-Positive Gastric and Gastroesophageal Junction Adenocarcinoma

Amgen Protocol Number AMG 910 20180292

Amendment Date: 14 October 2020

Rationale:

The protocol is being amended to harmonize content across all concerned countries following the separate national regulatory and ethics review processes. In addition, this amendment is intended to optimize study procedures to improve the operational efficiency of the protocol following investigator feedback. Furthermore, the protocol has been updated to reflect feedback from initial Dose Limiting Recommendation Meetings (DLRM) and incorporate feedback received from global regulatory authorities during the initial reviews for this study.

Changes in this amendment include (but are not limited to):

- Clarifications relating to observation periods that should be followed during the study.
- Clarifications of pregnancy testing timelines.
- Updated toxicology to include additional available data.
- Updated Benefit/Risk Assessment to include information related to COVID-19.
- Streamlining of End Of Study text.
- Update to inclusion criteria to add definition of coagulation function status required for study participation and to reflect that subjects should be able to use proton pump inhibitors.
- Update to exclusion criteria to exclude subjects with inherited bleeding disorders and subjects with heparin-induced thrombocytopenia and subjects requiring non-steroidal anti-inflammatory drugs during study treatment.

- Addition of text to reflect slot reservation process to ensure that the start of patient dosing will be staggered by at least 72 hours.
- Updates to other protocol-required therapies to reflect more detailed recommendations with regard to dexamethasone pretreatment.
- Updates to excluded treatments, medical devices and/or procedures during study period to reflect that recommended preventive vaccinations may be administered in the treatment-free intervals.
- Updates to multiple-subject cohorts text to include text indicating that sequential dosing of subjects by at least 72 hours should be employed to all subjects within a dose escalation cohort.
- Updates to include additional dose-limiting toxicity (DLT) definitions.
- Updates to dose adjustments and re-start at a lower dose level text to include addition of supplemental text and information from initial patient dosing experience.
- Addition of supplemental text to outline timings for pulse oximetry assessments.
- Protocol-specific anticipated serious adverse events was updated for consistency with Medical Dictionary for Regulatory Activities (MedDRA) coding. Indigestion was removed because it is not a preferred term (PT) in MedDRA and is addressed as dyspepsia instead. Similarly, chronic acid reflux was removed because it is not a PT in MedDRA and is addressed as gastroesophageal reflux disease instead.

Finally, corrections, as well as editorial and clarifying changes have been made throughout the protocol.

Amendment 1

Protocol Title: A Global Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of the Half-life Extended Bispecific T-cell Engager AMG 910 in Subjects With Claudin 18.2-Positive Gastric and Gastroesophageal Junction Adenocarcinoma

Amgen Protocol Number AMG 910 20180292

Amendment Date: 17 January 2020

Rationale:

The original protocol, dated 21 November 2019, was updated based on comments received from the FDA on the Investigational New Drug application, mainly:

- Clarified and added specific AE management instruction to Table 6-3 (Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of Adverse Events)
- Clarified that the Retreatment Group does not allow for any other anticancer therapies between stop of AMG 910 and AMG 910 re-treatment
- Clarified stopping rules for dose escalation
- Defined “active central nervous system metastases" in exclusion criterion 202 to mean "untreated or symptomatic active central nervous system metastases"
- Corrected for inconsistency in birth control language (revising time frame from 45 days after last dose of AMG 910 to 75 days for female subjects to be consistent with CTFG guidance, and 5 months for male subjects)
- Corrected for inconsistency in urinalysis assessments in Table 1-1 (Schedule of Activities)

In addition, administrative and typographical corrections were made as a result of this review.