Title Page

Protocol Title:		A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager AMG 757 in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer
Short Protocol Title:		A Phase 1b Study of AMG 757 in Subjects with Neuroendocrine Prostate Cancer
Protocol Number:		20200040
Investigational Product:		**Tarlatamab (AMG 757)**
Trade Name:		Not applicable
Sponsor	**Name of Sponsor:**	Amgen, Inc.
	Address:	One Amgen Center Drive Thousand Oaks, CA 91320
	Telephone Number:	+1 (805) 447-1000
Protocol Approver	**Name:**	[redacted] MD
	Function:	VP Early Development, TA Head Oncology
Key Sponsor Contact	**Name:**	[redacted] MD
	Address:	One Amgen Center Drive Thousand Oaks, CA 91320**, USA**
	Telephone Number:	[redacted]
	Email Address:	[redacted]

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Data Elements Standards Version:	6.0

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

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager AMG 757 in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer, dated **21 June 2024**, 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 sub-investigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager AMG 757 in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer

Short Protocol Title: A Phase 1b Study of AMG 757 in Subjects with Neuroendocrine Prostate Cancer

Study Phase: 1b

Indication: Adult subjects with de novo or treatment-emergent neuroendocrine prostate cancer

Rationale

Delta-like protein 3 (DLL3), a non-canonical Notch ligand, is a promising therapeutic target due to its high expression on the cell surface of small cell lung cancer (SCLC) and minimal, mainly cytoplasmic localization in normal tissues. DLL3 mRNA and protein are also highly expressed by other neuroendocrine tumor types, including neuroendocrine prostate cancer (NEPC). RNA sequencing of metastatic tumors showed that 100% (8/8) of NEPC tumors expressed DLL3 (MET500 database; Robinson et al, 2017). A separate study identified DLL3 as a gene expressed in 80% (12/15) of NEPC samples (Tsai et al, 2017). A recent study demonstrated that DLL3 protein is expressed in 76.6% (36/47) of neuroendocrine prostate tumors, and also in a subset of advanced metastatic prostate cancer (Puca et al, 2019).

Tarlatamab (International Nonproprietary Name [INN]; AMG 757) is a half-life extended (HLE) bispecific T-cell engager (BiTE®) antibody construct combining the binding specificities for DLL3 and cluster of differentiation 3 (CD3) genetically fused to the N-terminus of a single chain immunoglobulin G (IgG) fragment crystallizable (Fc; scFc) region. Currently, a first in human phase 1 study evaluating the safety, tolerability and pharmacokinetics of tarlatamab in subjects with SCLC (Study 20160323) is ongoing. Tarlatamab demonstrated potent cell killing against DLL3-expressing SCLC and other neuroendocrine tumor cell lines in vitro, including the NEPC cell line, NCI-H660. Tarlatamab demonstrates anti-tumor activity in small cell lung cancer (SCLC) and melanoma xenograft models of neuroendocrine tumors and can enable regression of established small cell lung tumors in mouse xenograft models. Therefore, targeting NEPC with tarlatamab may lead to anti-tumor activity.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of tarlatamab	• Treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, electrocardiogram (ECG), and clinical laboratory tests
• Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D)	• Dose limiting toxicities (DLTs)
Secondary	
• Evaluate anti-tumor activity of tarlatamab as assessed by additional measures	• Objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • Duration of response (DOR) per RECIST 1.1 • Radiographic progression-free survival (PFS) per Prostate Cancer Working Group 3 (PCWG3) • Overall survival (OS) • Disease Control Rate (DCR) per RECIST 1.1
• Characterize the pharmacokinetics (PK) tarlatamab	• PK parameters for tarlatamab following intravenous (IV) 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 ratio, and half-life ($t_{1/2}$)

Overall Design

This is an open label phase 1b study evaluating tarlatamab monotherapy.

Tarlatamab will be administered as a short-term intravenous (IV) infusion every 2 weeks (Q2W) (with step dosing) in a 28-day cycle as monotherapy therapy in subjects with de novo or treatment-emergent NEPC.

The study will consist of 2 parts: dose exploration (Part 1) and dose expansion (Part 2).

At the time of initiation of the study, the starting dose will be the highest dose deemed safe and tolerable in the ongoing phase 1 trial of tarlatamab in subjects with SCLC

(Note: based on emerging safety data from Study 20160323, the starting dose may be lower than the highest dose deemed safe and tolerable). The planned highest dose in this study is not anticipated to exceed the maximum tolerated dose (MTD) as established in the ongoing Study 20160323.

Based on emerging data from the tarlatamab monotherapy in this indication and emerging data from other trials with tarlatamab, the protocol may be amended to include a combination of tarlatamab with anti-PD-1 (L1) agent.

Number of Subjects

Approximately 60 subjects will be enrolled in this study. Up to 20 subjects will be enrolled in the dose exploration phase (Part 1) and 40 subjects will be enrolled in the dose expansion phase (Part 2). Based on emerging data in Part 2, the protocol may be amended to increase the sample size.

Summary of Subject Eligibility Criteria

Adult subjects (≥ 18 years of age) with metastatic de novo or treatment-emergent NEPC defined as one or more of the following will be eligible to enroll: histological diagnosis of small cell NEPC, prostate carcinoma with neuroendocrine differentiation as defined by positive immunohistochemical staining for chromogranin and/or synaptophysin in the majority of the tumor sample or ≥ 2 alterations in Tp53, RB1, and/or PTEN by immunohistochemistry (IHC) or genomic analyses of baseline tumor tissue or [redacted] Subjects are required to have progressed on at least 1 line of prior treatment, including a platinum containing regimen for de novo NEPC (if at the time of NEPC diagnosis they had no prior diagnosis or treatment for prostate carcinoma) or an androgen signaling inhibitor (eg, abiraterone, enzalutamide, and/or apalutamide) if treatment-emergent (had a previous diagnosis of prostate carcinoma prior to NEPC diagnosis). Subjects must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria with Prostate Cancer Working Group 3 (PCWG3) guidelines, have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, and adequate organ function.

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

Treatments

Tarlatamab is an Amgen investigational product used in this study. Tarlatamab will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

At the time of initiation of the study, the starting dose will be the highest dose deemed safe and tolerable in the ongoing phase 1 trial of tarlatamab in subjects with SCLC (Note: based on emerging safety data from Study 20160323, the starting dose may be lower than the highest dose deemed safe and tolerable). Tarlatamab will be administered as a short-term IV infusion (approximately 60 minutes followed by a flush) on day 1 and day 15 in a 28-day cycle (cycle 2 and beyond). To reduce the risk of cytokine release syndrome (CRS), premedication with dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) will be administered within 1 hour prior to all cycle 1 doses. In addition, step-dosing will be implemented (involving a run-in dose on cycle 1 day 1 followed by one [redacted] step doses) during cycle 1, prior to reaching a target dose. Prophylaxis with IV hydration 1 L normal saline over 4 to 5 hours immediately following all dose(s) in cycle 1 is required.

Sites are required to have tocilizumab or siltuximab (if tocilizumab not available) on site for potential treatment of CRS. Siltuximab stopping rules are found in Section 9.4.1.1.1. Tarlatamab will be dosed until disease progression (treatment beyond disease progression may be allowed per PCWG3 guidelines).

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage and administration of tarlatamab.

Procedures

Each subject will follow the same treatment schedule and procedural requirements.

After written informed consent has been obtained, all screening tests and procedures will be performed within 28 days of administration of tarlatamab (day 1), unless otherwise noted. Serial clinical safety and study evaluations as per the schedule of activities will be performed including physical examination, vital signs, clinical laboratory tests, radiological assessment, tumor biopsy, pharmacokinetics (PK), and biomarker sample collections.

All subjects will be hospitalized for intensive monitoring for 48 hours post tarlatamab infusion during all cycle 1 doses. Hospitalization is not required for cycle 2 unless a subject experiences grade 2 or higher CRS or neurological events in cycle 1 (minimum of 24 hours hospitalization required post tarlatamab infusion on cycle 2 day 1 if grade 2 or higher CRS or neurological events are noted in cycle 1). The subjects may be discharged after this period if there are no signs and symptoms of CRS or other acute

toxicities. If subjects are not hospitalized during cycle 2, subjects will be observed for 8 hours post tarlatamab infusion.

Routine radiological imaging (computed tomography [CT]/magnetic resonance imaging [MRI]) 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 per PCWG3 guidelines (Sections 11.8 and 11.9). To further assess the risk of delayed adverse events, the subject must return for safety follow-up (SFU) visit approximately **60** (+5) days after the last dose of tarlatamab.

Long-term follow-up will be conducted every 3 months up to 3 years from the first dose of tarlatamab 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.

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

Statistical Considerations

All subjects who are enrolled and receive at least 1 dose of tarlatamab will be included in the analysis, unless otherwise specified.

The primary analysis will occur when target enrollment is complete and each subject either completes at least 6 months on study or withdraws from the study. The final analysis will be performed after the last subject has had an opportunity to complete the corresponding end of treatment visit/procedures.

Descriptive statistics will be provided for selected demographics, safety, pharmacokinetic, efficacy 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. The number and percentage of subjects reporting any treatment-emergent adverse events will be tabulated. Clinical laboratory tests, physical examination findings and vital sign data will be listed. Summaries of laboratory, examination and vital sign data over time and/or changes from baseline over time will be provided.

Confidence intervals (CI) for proportions will be estimated using an exact method proposed by Clopper-Pearson (Clopper and 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 (Brookmeyer and Crowley, 1982) method.

Kaplan-Meier methods will be used to estimate landmarks for time to event endpoints with the Greenwood formula (Kalbfleisch and Prentice, 1980) used to estimate the standard error used in CI calculation.

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

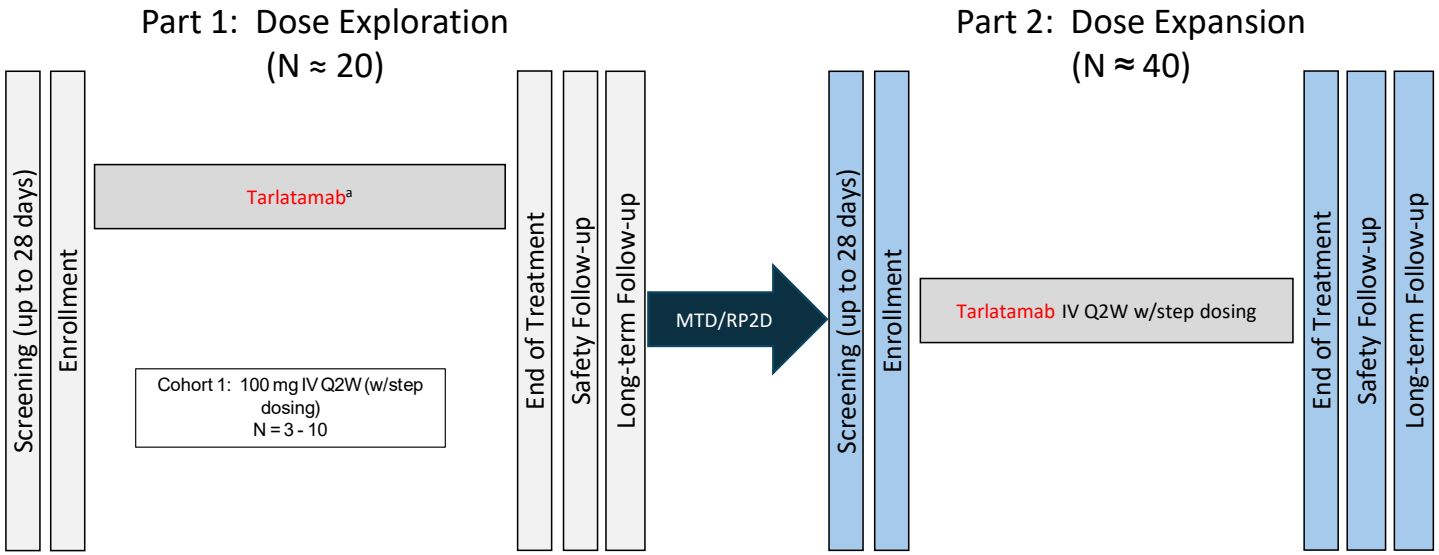
Statistical Hypotheses

No formal statistical hypotheses will be tested in this phase 1b study.

Sponsor Name: Amgen, Inc.

1.2 Study Schema

Figure 1-1. Study Schema



DLT = dose limiting toxicity; IV = intravenous; MTD = maximum tolerated dose; Q2W = every 2 weeks; RP2D = recommended phase 2 dose

[a] At the time of initiation of the study, the starting dose will be the highest dose deemed safe and tolerable in the ongoing phase 1 trial of tarlatamab in subjects with small cell lung cancer (Note: based on emerging safety data from Study 20160323, the starting dose may be lower than the highest dose deemed safe and tolerable). The planned highest dose in this study is not anticipated to exceed the MTD as established in the ongoing Study 20160323. The dose escalation scheme shown here is an example and the actual dose escalation schema will be based on what is established in the ongoing Study 20160323 (please refer to Table 4-1 for planned doses per dose cohort level in Study 20160323). In order to consider a certain Dose Level as the MTD at least 6 DLT evaluable subjects must be enrolled at that dose level. No more than 10 DLT evaluable subjects will be enrolled at any specific dose level in dose exploration phase.

Study Periods:

- Screening: up to 28 days before enrollment
- Treatment: treatment continues until progression
- End of treatment: should occur as soon as possible (within 14 days) after the last dose of investigational product
- Safety follow-up: approximately **60** (+5) days after the end of the last dose of tarlatamab
- Long-term follow-up: every 3 months up to 3 years from the first dose of protocol-required therapy for all subjects who have not withdrawn consent

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities: Single Step Dosing - Cycle 1 Only

STUDY PERIOD/ TREATMENT CYCLE	SCR[a]	Cycle 1 only																				
WEEK[b]	-4 to -1	1							2						3							4
DAY[b]	-28 to -1	1				2	3	5	8				9	10	15						16	17	22
HOUR (relative to infusion)[c]		Pre	EOI	2	6	24	48	96	Pre	EOI	2	6	24	48	Pre	EOI	2	6	24	48	168
General/Safety Assessments																						
Informed consent	X																					
Clinical Evaluation[d]	X	X				X	X	X	X				X	X	X				X	X	X	
Vital signs, pulse ox[e]	X	X	X		X[e]		X	X	X	X		X[e]		X	X	X		X[e]		X	X	
12-lead ECG[f]	X	X	X						X	X					X	X						
ECHO or MUGA[jj]	X																					
AE review			☐==========																			
SAE review	☐==========																					
Prior/concomitant medication	☐==========																					
Local Laboratory Assessments																						
CBC with differential	X	X[g]				X	X	X	X				X	X	X				X	X	X	
Coagulation	X	X[g]				X		X	X				X	X	X				X		X	
Chemistry panel[h]	X	X[g]			X	X	X	X	X				X	X	X				X	X	X	
Lipase and Amylase	X	X[g]																				
Urinalysis	X																					
Safety endocrine panel[i]	X	X[g]																				
CRP	X	X[g]			X	X	X		X			X	X	X	X			X	X	X	X	
Ferritin	X	X[g]			X	X	X		X			X	X	X	X			X	X	X	X	
HBsAg, HBsAb, HCV Ab, HIV	X																					
Central and Biomarker Laboratory Tests																						
Cytokines		X		X[j]	X	X	X		X			X	X	X	X			X	X	X		
[redacted]																						

Footnotes following last page of Table 1-2

Table 1-1. Schedule of Activities: Single Step Dosing - Cycle 1 Only

STUDY PERIOD/ TREATMENT CYCLE	SCR[a]	Cycle 1 only																			
WEEK[b]	-4 to -1	1							2						3						4
DAY[b]	-28 to -1	1				2	3	5	8				9	10	15				16	17	22
HOUR (relative to infusion)[c]		Pre	EOI	2	6	24	48	96	Pre	EOI	2	6	24	48	Pre	EOI	2	6	24	48	168
Central and Biomarker Laboratory Tests (continued)																					
[redacted]																					
Pharmacogenetics (optional)[p]		X																			
Pharmacokinetics Assessments																					
Tarlatamab PK Collection[q]		X	X		X	X	X		X	X		X	X	X	X	X		X	X	X	X
Study Drug Treatment																					
Dexamethasone or equivalent[r]		X							X						X						
Tarlatamab IV infusion[s]			X							X						X					
IV hydration 1 L[s]			X							X						X					
Hospital stay[t]		□==========□							□==========□						□==========□						
Imaging Assessments: See Table 1-3 Schedule of Imaging Assessments																					

Footnotes following last page of Table 1-2

Table 1-2. Schedule of Activities: Cycle 2 and Beyond

STUDY PERIOD/TREATMENT CYCLE	Cycle 2															Q cyc[u]		Q2 cyc[v]	Q3 cyc[w]	EOT	SFU[x]	LTFU[ff]
WEEK[b]	1							2	3						4	1	3	1	1			
DAY[b]	1				2	3	5	8	15				16	17	22	1	15	1	1			
HOUR (relative to infusion)[c]	Pre	EOI	2	6	24	48	96	168	Pre	EOI	2	6	24	48	168							
General/Safety Assessments																						
Clinical Evaluation[d]	X				X	X	X	X	X				X	X	X	X	X			X	X	
Vital signs, pulse ox[e]	X	X			X	X	X	X	X	X			X	X	X	X	X			X	X	
12-lead ECG[f]	X[y]	X[y]							X[y]	X[y]						X[y]	X[y]					
AE review	□==========□																					
SAE review	□==========□																					
Prior/concomitant medication	□==========□																					
Local Laboratory Assessments																						
CBC with differential	X				X	X		X	X				X	X	X	X	X			X	X	
Coagulation	X				X			X	X				X		X	X	X			X	X	
Chemistry panel[h]	X			X	X	X	X	X	X				X	X	X	X	X			X	X	
Lipase and Amylase	X															X					X	
Urinalysis																		X				
Safety endocrine panel[i]	X															X				X	X	
CRP	X			X	X	X		X	X			X	X	X	X	X	X			X	X	
Ferritin	X			X	X	X		X	X			X	X	X	X	X	X			X	X	
HBsAg, HBsAb, HCV Ab, HIV																						
Central and Biomarker Laboratory Tests																						
Cytokines	X			X	X	X			X			X	X	X		X[z]						
[redacted]																						

Footnotes following last page of Table 1-2

Table1-2. Schedule of Activities: Cycle 2 and Beyond

STUDY PERIOD/TREATMENT CYCLE	Cycle 2															Q cyc[u]		Q2 cyc[v]	Q3 cyc[w]	EOT	SFU[x]	LTFU[ff]
WEEK[b]	1							2	3						4	1	3	1	1			
DAY[b]	1				2	3	5	8	15				16	17	22	1	15	1	1			
HOUR (relative to infusion)[c]	Pre	EOI	2	6	24	48	96	168	Pre	EOI	2	6	24	48	168							
Central and Biomarker Laboratory Tests (continued)																						
[redacted]																						
Pharmacokinetics Assessments																						
Tarlatamab 757 PK Collection[q]	X	X		X	X	X		X	X	X		X	X	X	X	X[cc]	X[cc]				X	
Study Drug Treatment																						
Tarlatamab IV infusion[s]		X								X						X	X					
Imaging Assessments: See Table 1-3 Schedule of Imaging Assessments																						
Long-term Follow-up																						
Survival Status and/or subsequent cancer therapy[dd]																						X

Footnotes following last page of Table 1-2

Abbreviations used: Ab = antibody; ACTH = adrenocorticotropic hormone; AE = adverse event; BP = blood pressure; C = cycle; CBC = complete blood count; [redacted] CNS = central nervous system; COVID-19 =Coronavirus Disease 2019; CRP = C-reactive protein; CRS = Cytokine Release Syndrome; [redacted] D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOI = end of infusion; EOT = end of treatment; [redacted] FSH = follicle stimulating hormone; FT4 = free thyroxine; HBsAg = hepatitis B surface antigen; HBsAb = anti-hepatitis B surface antibody; HCV = hepatitis C; HIV = human immunodeficiency virus; HR = heart rate; IHC = immunohistochemistry; IGF-1 = insulin-like growth factor 1; IP = investigational product; IPIM = Investigational Product Instruction Manual; IV = intravenous; [redacted] LH = luteinizing hormone; LTFU = long-term follow-up; MMSE = Mini Mental Status Examination; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NE = neuroendocrine; [redacted] PCWG3 = Prostate Cancer Working Group 3; PD = progressive disease; PK = pharmacokinetic; Pre = pre-infusion; [redacted] PTEN = phosphatase and tensin homolog; Q cyc = every cycle; Q2 Cyc = every 2 cycles; Q3 Cyc = every 3 cycles; RB1 = retinoblastoma protein; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SAE = serious adverse event; SCR = screening; SFU = safety follow-up; SOA = Schedule of Activities; SOI = start of infusion; TLS = tumor lysis syndrome; Tp53 = tumor protein p53; TSH = thyroid stimulating hormone

a All screening procedures should be performed within 28 days prior to cycle 1 day 1 dosing.

b Each visit week and day is relative to day 1 of each cycle. Cycle 1 and cycle 2 visits have a ± 1-day window from designated time point unless otherwise specified. All subsequent visits beginning in cycle 3 will have a ± 3-day window.

c
- End of infusion (EOI) assessments or procedures are to be completed immediately after infusion of tarlatamab. EOI indicates the time when the IP infusion and saline flush is completed. Assessments after EOI indicate the time relative to EOI. Investigational product infusions are marked in the EOI column.
- Assessments are done pre-infusion unless specified.
- Laboratory assessments that were done within 24 hours prior to infusion do not need to be repeated (except for cycle 1 day 1 dosing where laboratory assessments should be collected within 4 hours before cycle 1 day 1 dosing of tarlatamab).
- All assessments and procedures should be collected at the exact nominal time point as noted in the Schedule of Activities. If unable to perform a procedure at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time.

d Clinical evaluation including physical exam, ECOG, weight and neurological exams, writing test, and MMSE (neurology specialty consultation service as clinically indicated). Performed at Screening only: demographics, medical history, and height. Clinical evaluation should be completed within 6 hours prior to the first dose of tarlatamab. On days 3, 10 and 17 of cycle 1 and beginning at cycle 2 and beyond, writing tests and MMSE are not required unless clinically indicated.

e Vital signs (BP, HR, RR, temperature) and pulse oximetry will be assessed. During and after each tarlatamab-infusion for the first cycle and if applicable on cycle 2 day 1 (during the hospitalization period [see Footnote r]), vital signs should be assessed accordingly during the following time points:
- Every 15 minutes (± 5 minutes) from start of infusion (SOI) and for the first 1-hour after EOI
- Every 30 minutes (± 5 minutes) from 2-4 hours EOI (at 2, 2.5, 3, 3.5, and 4 hours after EOI)
- Every hour (± 5 minutes) from 5-8 hours EOI (at 5, 6, 7, and 8 hours after EOI)
- Every 2 hours (± 5 minutes) from 9-16 hours EOI (at 10, 12, 14, and 16 hours after EOI)
- Every 4 hours (± 5 minutes) from 17-24 hours EOI (at 20 and 24 hours after EOI)

After 24 hours EOI, vital signs, and pulse oximetry should be assessed per institutional standards. For subjects not hospitalized in cycle 2, vital signs should be assessed for up to 8 hours (as above). **For cycle 3 and beyond, sites are to follow institutional guidelines for vital signs collection during and after infusion.**

f ECGs will be collected as single read and will be considered as safety ECGs.

g Lab should be collected within 4 hours before C1D1 dosing of tarlatamab.

h For cycles 1 and 2 only, please collect LDH and uric acid along with the chemistry panel for TLS monitoring (see Section 11.2).

i Safety endocrine panels: Cortisol, TSH, FT4, FSH, LH, testosterone will be evaluated at screening, day 1 of every cycle, EOT, and SFU. ACTH, prolactin, and IGF-1 will be evaluated only at screening and EOT.

j Cytokines (serum) on day 1 hour 2 will be collected for cycle 1 only.

[redacted]

p Pharmacogenetic (optional) sample obtained from cell pellet from a biomarker plasma sample at pre-dose (day 1) during cycle 1 only.

q For visits when subjects are dosed, PK samples should be collected within ± 30 min of the scheduled time points; pre-dose and EOI PK samples should be collected within 30-minutes pre-dose and within 30-minutes post EOI, respectively. For all other non-dosing visits, please follow the window given for procedures stated in Footnote b.
Note: It is important to document the exact time of IP administration and PK collection in the eCRF.

r Dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) will be administered within 1 hour prior to all doses (including all step dose[s]) of tarlatamab for cycle 1 only.

s Tarlatamab short-term IV infusion over 60 minutes and a flush. See IPIM for dose administration details. Prophylaxis with IV hydration 1 L normal saline over 4 to 5 hours immediately following all dose(s) in cycle 1 is required.

t All subjects will be hospitalized for intensive monitoring for 48 hours post tarlatamab infusion during all cycle 1 doses. Hospitalization is not required for cycle 2 unless a subject experiences grade 2 or higher CRS or neurological events in cycle 1 (minimum of 24 hours hospitalization required post tarlatamab infusion on C2D1 if grade 2 or higher CRS or neurological events are noted in cycle 1). The subjects may be discharged after this period if there are no signs and symptoms of cytokine release syndrome or other acute toxicities. If subjects are not hospitalized during cycle 2, subjects will be observed for 8 hours post tarlatamab infusion.

u Q Cyc: Collected at specified time point beginning with cycle 3 and at each subsequent cycle unless otherwise specified.

v Q2 Cyc: Collected every 2 cycles starting from cycle 3: C3D1, C5D1, C7D1, C9D1, C11D1

w Q3 Cyc: Collected every 3 cycles starting from cycle 4: C4D1, C7D1, C10D1

x SFU visit should be completed **60** (+5) days from the last dose of tarlatamab. For details regarding the tests and procedures to be completed for SFU please refer to Section 8.1.3.

y For cycles 2, 3, and 4 only: please collect ECG at pre- and post-infusion. No further ECGs are collected after cycle 4.

z Cytokines: after Cycle 2, collect only at Cycles 3 & 4 pre-dose

[redacted]

cc For cycles 3 and 4, collect PK samples at pre- and post-infusion. For all remaining cycles beginning with cycle 5 through 12, collect at pre-infusion only. PK samples will be collected only until end of cycle 12.

dd LTFU will be conducted every 3 months for 3 years from the first dose of tarlatamab on 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

ee For subjects who develop COVID19 during screening period and following screening Echo or MUGA, consider repeating Echo or MUGA following resolution

ff During the LTFU phase SAEs suspected to be related to IP that the investigator becomes aware of will be reported to Amgen **immediately and no later than** the 24 hours following the investigator's awareness of the event. **After the end of study, SAEs suspected to be related to IP will be reported to Amgen. Refer to Section 8.2.4.1.3 for additional details. Concomitant medication will not be collected during LTFU**

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

	SCR[a]	Treatment Period[b]	EOT	SFU	LTFU	Notes
MRI brain	X					All subjects must have MRI of the brain performed within 28 days prior to the first dose of tarlatamab. 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
CT/MRI, bone scan[c], and tumor burden assessment[d]	X	Every 8 weeks	X	X	X[e]	Radiologic imaging (CT/MRI) is required at the EOT or SFU visit if the subject has not had radiologic imaging performed within 6 weeks of the visit. Planar bone scintigraphy should be performed using conventional ^{99m}Tc-MDP radionuclide, or other equivalent ^{99m}Tc-labeled radiotracers.
[redacted]						

^{18}F-DCFPyL = 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ^{99m}; ^{18}F-FDG = fluorodeoxyglucose; [redacted] ^{99m}Tc-MDP = ^{99m}technetium methylene diphosphonate; CT = computed tomography; EOT = end of treatment; [redacted] LTFU = long-term follow-up; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Working Group 3; [redacted] SCR = screening; SFU = safety follow-up

[a] Results of imaging assessments conducted as standard of care may be use for screening within 30 days of start of study treatment.

[b] Timing is based on first dose of Tarlatamab (cycle 1 day 1) ± 7 days for imaging assessments.

[c] Per PCWG3 recommendations, the first post-treatment bone scan (at week 8) will be used as the baseline scan with which all future bone scans are compared.

[d] Radiologic imaging and tumor assessments are required at screening and every 8 ± 1 weeks post-therapy initiation until clinically significant disease progression or deterioration, withdrawal of consent or start of new anticancer therapy. Every assessment must include the chest, abdomen, and pelvis, all other known sites of disease and MRI of the brain if a subject has signs or symptoms suggestive of CNS metastases. The MRI/CT can be obtained earlier if clinical deterioration necessitates an earlier scan at the discretion of the managing physician. The same contrast and modality used at screening should be used for all subsequent assessments. 99mTc-MDP bone scan is required for each radiologic imaging and tumor assessment. Tumor burden assessments will be performed based on PCWG3 guidelines (Sections 11.8 and 11.9). To confirm soft tissue disease progression, a second MRI/CT scan must be performed at least 4 weeks after the first detection of soft tissue disease progression. Confirmation of bone disease progression by bone scan should be performed per PCWG3 guidelines. Responses require confirmation by a repeat consecutive assessment at least 4 weeks after the first detection of response as measured by RECIST 1.1.

[e] For subjects who discontinued treatment for any reason other than confirmed PD, every effort should be made to perform radiographic imaging (CT/MRI/bone) of the chest, abdomen, pelvis, bone, and all other known sites of disease every 3 months until documentation of confirmed PD per PCWG3 guidelines, clinical progression, start of new anticancer therapy, or up to 3 years after the first dose of tarlatamab, whichever occurs first.

[redacted]

2. Introduction

2.1 Study Rationale

Delta-like protein 3 (DLL3), a non-canonical Notch ligand, is a promising therapeutic target due to its high expression on the cell surface of small cell lung cancer (SCLC) and minimal, mainly cytoplasmic localization in normal tissues. DLL3 mRNA and protein are also highly expressed by other neuroendocrine tumor types, including neuroendocrine prostate cancer (NEPC). RNA sequencing of metastatic tumors showed that 100% (8/8) of NEPC tumors expressed DLL3 (MET500 database; Robinson et al, 2017). A separate study identified DLL3 as a gene expressed in 80% (12/15) of NEPC samples (Tsai et al, 2017). A recent study demonstrated that DLL3 protein is expressed in 76.6% (36/47) of neuroendocrine prostate tumors, and also in a subset of advanced metastatic prostate cancer (Puca et al, 2019).

Tarlatamab is a half-life extended (HLE) bispecific T-cell engager (BiTE®) antibody construct combining the binding specificities for DLL3 and cluster of differentiation 3 (CD3) genetically fused to the N-terminus of a single chain immunoglobulin G (IgG) fragment crystallizable (Fc; scFc) region. Currently, a first in human phase 1 study evaluating the safety, tolerability and pharmacokinetics of tarlatamab in subjects with SCLC (Study 20160323) is ongoing. Tarlatamab demonstrated potent cell killing against DLL3-expressing SCLC and other neuroendocrine tumor cell lines in vitro, including the NEPC cell line, NCI-H660. Tarlatamab demonstrates anti-tumor activity in small cell lung cancer (SCLC) and melanoma xenograft models of neuroendocrine tumors and can enable regression of established small cell lung tumors in mouse xenograft models. Therefore, targeting NEPC with tarlatamab may lead to anti-tumor activity.

2.2 Background

2.2.1 Disease

Prostate cancer is the most frequently diagnosed non-cutaneous cancer in men with an estimated 191 930 new cases and 33 330 deaths in the United States (US) in 2020 (American Cancer Society, 2020). In the European Union **(EU)**, there were an estimated 365 000 new cases of prostate cancer in 2015, with 72 000 and 77 000 deaths estimated in 2012 and 2015, respectively (10% of total cancer deaths) (Crocetti, 2015). NEPC represents an aggressive variant of prostate cancer. While de novo cases appears to be rare, accounting for less than 2% of patients at the time of initial diagnosis (Parimi et al, 2014), treatment-emergent NEPC, characterized by a histological transformation from adenocarcinoma to a high-grade neuroendocrine tumor, is becoming increasingly

recognized and may develop in 15% to 20% of patients treated with standard therapies for prostate adenocarcinoma, including novel hormonal therapies (Aggarwal et al, 2018). The exact mechanisms underlying this histological transformation are unclear, however, loss of androgen signaling dependence and the acquisition of alternative lineage programs have been associated with the development of NEPC. Overall, the prognosis for NEPC is poor (Wang et al, 2014) and is often treated with platinum-based chemotherapy regimens (Aparicio et al, 2013). There is currently no standard therapeutic approach and it remains an unmet need.

2.2.2 Amgen Investigational Product Background: Tarlatamab

BiTE® (bispecific T-cell engager) molecules have been designed to direct T effector memory cells towards target cells. BiTE® binding to T-cells and target cells triggers target cell specific cytotoxicity which closely resembles standard cytotoxic T lymphocyte activation.

Tarlatamab is an HLE BiTE® antibody construct combining the binding specificities for delta like ligand 3 (DLL3) and CD3 genetically fused to the N-terminus of a single chain IgG Fc (scFc) region. Tarlatamab is being developed with the intent to treat patients with SCLC.

Refer to the specific section of the Investigator Brochure (IB) for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

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

2.2.2.1 Pharmacology

The activity of tarlatamab requires the simultaneous binding to both DLL3 expressed on target cells and CD3 expressed on T-cells. Bispecific binding of BiTE® antibody constructs, such as tarlatamab, causes the formation of a cytolytic synapse between T-cells and target cells. This has been exemplified using an epithelial cell adhesion molecule (EpCAM)-specific BiTE® antibody construct (Offner et al, 2006).

Tarlatamab treatment induces T-cell activation and expansion, and redirects cytotoxic $CD8^+$ or $CD4^+$ T lymphocytes to kill $DLL3^+$ cells. The 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.

Tarlatamab-mediated T-cell activation not only induces the directed release of cytotoxic proteins to target cells, but also results in a transient production of inflammatory

cytokines such as tumor necrosis factor (TNF), interferon gamma (IFN-γ) and interleukin-2 (IL-2) by T-cells. In vitro studies demonstrated that cytokine release by tarlatamab-activated T-cells is attenuated by corticosteroids, but this can be accompanied by a slight reduction in cytotoxic potency (Amgen Study Report 122718).

Tarlatamab is a potent molecule showing mean half-maximal lysis of human SCLC cell lines by human effector cells in vitro over a range of [redacted] pM. Tarlatamab monotherapy induced regression of established SCLC primary tumors and liver metastases in orthotopic mouse models, with evidence for BiTE® target engagement and increased T-cell infiltration and proliferation in tumors (Amgen Study Report [redacted] Tarlatamab also demonstrates cytotoxic activity against other DLL3-expressing neuroendocrine cell lines, including the NEPC cell line NCI-H660.

2.2.2.2 Toxicology

The cynomolgus monkey was chosen to evaluate the nonclinical safety of tarlatamab because both the CD3 and DLL3 binding moieties of tarlatamab cross-reacted with similar high affinities to the analogous human and cynomolgus monkey antigens. The potential toxicity of tarlatamab was evaluated in Good Laboratory Practice (GLP) compliant 28-day cynomolgus monkey toxicology studies. In the 28-day study, tarlatamab was administered once weekly by intravenous (IV) infusion at 0, 50, 500, and 4500 µg/kg. Tarlatamab-related changes were limited to a minor decrease in lymphocyte populations (detected after the second dose only) at 4500 µg/kg, a slightly increased heart rate (on day 2 but not at day 23) at ≥ 500 µg/kg, and a minimal to mild mixed inflammatory cell infiltrate in the pituitary at 50 µg/kg and 500 µg/kg. There was no evidence of tissue injury associated with the infiltrate. A dose-related increase in incidence of anti-drug antibodies (ADAs) was detected. One animal had vascular injury-associated changes in the heart and lung that were consistent with secondary effects likely mediated by ADA-related immune complexes (ADA-IC). It is important to note that the production of ADAs in animals is not predictive of a potential for antibody formation in humans. All tarlatamab-related effects exhibited full or partial reversibility and all changes were considered not adverse. In the 3-month study, AMG 757-related clinical pathology changes were limited to a minimal decrease in lymphocytes at 4500 µg/kg. In addition, AMG 757-related changes were observed in the pituitary gland at ≥ 50 µg/kg, characterized as a minimal to mild mononuclear cell infiltrate composed primarily of lymphocytes, with no evidence of tissue injury. The Highest Non-Severely

Toxic Dose (HNSTD) was determined to be 4500 µg/kg in both the 28-day and 3-month studies based on the absence of any AMG 757-related adverse findings.

2.2.2.3 Background Clinical Experience With Amgen Investigational Product Tarlatamab

As of the 15 April 2021 data cutoff, 91 subjects were enrolled in the tarlatamab first-in-human (FIH) Study 20160323, 88 (96.7%) of whom received at least 1 dose of tarlatamab. Seventy subjects received monotherapy: 1 subject each was assigned 0.003, 0.01, 0.03, and 0.1 mg of tarlatamab; 12 subjects were assigned 0.3 mg; 8 subjects were assigned 1 mg; 11 subjects were assigned 1 to 3 mg; 10 subjects were assigned 1 to 10 mg; 8 subjects were assigned 1 to 30 mg; 13 subjects were assigned 1 to 100 mg; and 4 subjects were assigned 1 to 25 to 100 mg of tarlatamab monotherapy administered intravenously (IV) every 2 weeks (Q2W). Overall, all subjects (100%) had treatment emergent adverse events (TEAEs); the most commonly reported adverse events were cytokine release syndrome (31 subjects [44.3%]); pyrexia (22 subjects [31.4%]); fatigue (18 subjects [25.7%]); constipation (17 subjects [25.7%]); nausea (16 subjects [24%]); anemia (12 subjects [17.1%]); and dysgeusia and dyspnea (11 subjects each [15.7%]). Serious adverse events were reported for 33 subjects (47.1%), treatment related adverse events leading to withdrawal from tarlatamab were reported for 3 subjects (3%), and grade ≥ 3 treatment-emergent adverse events (TEAEs) were reported for 34 subjects (48.6%). One subject (1.4%), who received 2 doses of tarlatamab at 0.3 mg IV Q2W, had a treatment-emergent fatal adverse event of pneumonitis, which was considered to be a dose-limiting toxicity (DLT) event.

Cytokine release syndrome (CRS) is the most frequently reported adverse event occurring in 31 subjects (44.3%) with grade 2 CRS occurring in 7 subjects (10%) and grade 3 CRS occurring in 1 subject (1.4%). No grade 4 or higher CRS has been reported at the time of the data cutoff date. CRS presented mainly as fever, tachycardia, nausea and fatigue ± hypotension and was reversible. In 8 subjects (11.4%), CRS was reported as a serious adverse event, 1 event of which led to treatment discontinuation. CRS occurred predominantly following the first 2 doses of tarlatamab in cycle 1 (CRS typically did not recur in subsequent cycles following cycle 1), and was managed with supportive care and corticosteroids.

Based on emerging data, neutropenia has been reported in the FIH study. As of 28 July 2021, with a total of 113 subjects (112 subjects in Study 20160323 and 1 subject

in Study 20200040) exposed, treatment-emergent neutropenia or neutrophil count decreased was observed in 11 subjects (9.7%). Out of the 11 subjects, 3 subjects (2.7%) experienced grade 2 adverse events, 3 subjects (2.7%) experienced grade 3 events, and 5 subjects (4.4%) experienced grade 4 neutropenia events. There were no fatal neutropenia events. One subject experienced 2 serious adverse events of neutropenia (Grade 3 and Grade 4). Tarlatamab was interrupted in 3 subjects (one subject discontinued), and it was withdrawn in 2 subjects. There were no cases of febrile neutropenia.

As of 15 April 2021, a preliminary efficacy data was available for 69 subjects who received monotherapy. Overall, a confirmed PR was observed starting at a dose level of 0.3 through 100 mg in a total of 12 subjects for an overall ORR (95% CI) of 17.4% (9.3, 28.4). The disease control rate (95% CI) was 46.4% (34.3, 58.8).

Eight subjects received combination therapy with pembrolizumab in Part C of the ongoing FIH Study 20160323 with 5 subjects assigned 0.1 mg and 3 subjects assigned 0.3 mg of tarlatamab. Cohort 16 with 0.3 mg of tarlatamab administered over 1-hour Q2W [redacted] As of 15 April 2021, 8 (100%) subjects had TEAEs, 3 (37.5%) subjects had serious TEAEs, 3 (37.5%) subjects had grade ≥ 3 TEAEs, 0 (0%) subjects had TEAEs that led to treatment discontinuation. The most common adverse events include: fatigue (5 subjects [62.5%]), nausea (4 subjects [50.0%]), decreased appetite (3 subjects [37.5%]), vomiting (3 subjects [37.5%]), constipation (2 subjects [25.0%]), contusion (2 subjects [25.0%]), dyspnea (2 subjects [25.0%]), headache (2 subjects [25.0%]), insomnia (2 subjects [25.0%]), myalgia (2 subjects [25.0%]), and pyrexia (2 subjects [25.0%]). Cytokine release syndrome was reported in 1 (13%) subject (grade 2 CRS event which occurred on cycle 1 day 1 following administration of tarlatamab as monotherapy).

Ten subjects received a CRS mitigation strategy in Part D of the ongoing FIH Study 20160323 consisting of 1 to 100 mg tarlatamab plus dexamethasone. Eight subjects (80.0%) reported a TEAE. Grade 3 adverse events were reported for 5 subjects (50.0%). Adverse events by preferred term reported for ≥ 20.0% of subjects were CRS (6 subjects [60.0%]), pyrexia (3 subjects [30.0%]), dysgeusia (3 subjects [30.0%]), and fatigue, constipation, hyponatremia, chills, and decreased neutrophil count (each 2 subjects [20.0%]). Reported CRS of grade ≥ 2 was reported in 2 subjects (20.0%). Serious CRS was reported in 2 subjects (20.0%).

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

As of 26 February 2021, preliminary PK data for tarlatamab were available for 68 subjects (61 subjects from monotherapy cohorts and 7 subjects from the pembrolizumab combination cohorts).

Within the evaluated target dose range of 0.003 to 100 mg Q2W (with or without one step dosing paradigm), the serum tarlatamab exposures increased in an approximate dose proportional manner with mean estimated $t_{1/2}$ at steady state ranging from [redacted]. Approximate steady state in serum tarlatamab exposures was achieved within 4 weeks of every other week target regimen initiation.

2.3 Benefit/Risk Assessment

Delta-like protein 3 (DLL3), a non-canonical Notch ligand, is a promising target for the development of T-cell directed therapies due to its high expression on the cell surface of neuroendocrine tumor cells, and minimal, mainly cytoplasmic localization in normal tissues. RNA sequencing of metastatic tumors showed that 100% (8/8) of NEPC tumors expressed DLL3 (MET500; Robinson et al, 2017). A separate study identified DLL3 as a gene expressed in 80% (12/15) of NEPC samples (Tsai et al, 2017). A recent study found enhanced expression of DLL3 in advanced metastatic prostate cancer, particularly in neuroendocrine prostate cancer (NEPC) (Puca et al, 2019). Tarlatamab demonstrated potent cell killing against neuroendocrine tumor cells in vitro and can enable regression of established small cell lung tumors in mouse xenograft models. Therefore, targeting NEPC with tarlatamab may lead to anti-tumor activity. NEPC is considered a clinically aggressive variant of advanced prostate cancer with poor responses to standard treatments and limited therapeutic options.

The key safety information for tarlatamab including risk, summarized in Table 2-1 below, are based on experience with tarlatamab in the phase 1, FIH Study 20160323 for the indication SCLC, on the biological mechanism of action, based on experience with other BiTE® molecules, and on the potential for on-target, off-tumor effect. The additional potential safety concerns of neurological events, pituitary dysfunction, tumor lysis syndrome (TLS), and renal toxicity is summarized in the sections below. Neutropenia has also been observed in the FIH study and is considered an identified risk.

Table 2-1. Key Risks for Tarlatamab

Safety Risk	Description
Cytokine Release Syndrome (CRS)	CRS is a recognized adverse drug reaction of tarlatamab administration due to safety data from tarlatamab phase 1 first in human Study 20160323 for the indication SCLC. CRS is a systemic inflammatory response characterized by a release of cellular cytokines. CRS is risk of T-cell directed therapies. CRS is a risk associated with therapy with the approved BiTE® molecule, blinatumomab (anti-CD19 BiTE® antibody construct) in patients with acute lymphoblastic leukemia (ALL) and is associated also with other BiTE® molecules currently in development for treatment of solid and hematologic cancers. Clinical signs and symptoms of CRS may include the following: • Constitutional – fever ± rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache • Skin – rash • Gastrointestinal – nausea, vomiting, diarrhea • Respiratory –dyspnea, tachypnea, hypoxemia • Cardiovascular – tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late) • coagulation: elevated D-dimer, hypofibrinogenemia ± bleeding • renal: azotemia • hepatic: transaminitis, hyperbilirubinemia Infusion reactions may be clinically indistinguishable from manifestations of CRS. .
Neutropenia	Neutropenia has been observed in patients receiving tarlatamab. The risk mitigation plan includes monitoring of laboratory parameters (including, but not limited, to white blood cell count and absolute neutrophil count) which will be evaluated at baseline and monitored throughout the study. Specific recommendations for the management of neutropenia, and infusion interruption and stopping rules are found in Table 6-4.

ALL = acute lymphoblastic leukemia; BiTE® = bispecific T-cell engager; CD19 = cluster of differentiation 19; CRS = cytokine release syndrome; SCLC = small cell lung cancer.

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

A clinical safety monitoring and mitigation strategy with emphasis on cytokine release syndrome, neurological toxicities, and pituitary dysfunction will be implemented in this study which will include but not be limited to prevention, ongoing monitoring, early recognition, and prompt management. Refer to Section 6.8 for detailed management recommendations.

Given the evidence provided above, and with the mitigations and safety monitoring built into the protocol, the potential benefits to the patient are believed to outweigh the risks.

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

2.3.1 Additional Potential Safety Concerns for Tarlatamab

2.3.1.1 Neurological Events

There exists the risk of neurological adverse events with administration of AMG 757. Very low levels of DLL3 expression have been detected in the brain. In addition, a wide range of commonly observed neurological symptoms have been associated with the use of the approved BiTE molecule, blinatumomab (anti-CD19 BiTE antibody construct) in patients with acute lymphoblastic leukemia (ALL). The spectrum of neurologic events associated with blinatumomab has not been observed in clinical trials for other BiTE molecules, and the neurotoxicity may in part be associated with targeting CD19. Neurological events have been observed with AMG 757 administration in the AMG 757 phase 1 FIH Study 20160323 for the indication SCLC. No neurologic events were observed in the AMG 757 28-day and 3-month GLP toxicology studies in cynomolgus monkeys.

2.3.1.2 Pituitary Dysfunction

There exists the risk of pituitary dysfunction with administration of AMG 757. The target DLL3 protein is expressed in the pituitary and there were observations of an AMG 757-related mixed inflammatory cell infiltrate in the pituitary in the 28-day and 3-month GLP cynomolgus monkey toxicology studies.

2.3.1.3 Tumor Lysis Syndrome

Tumor lysis syndrome, a severe, life-threatening disorder that can occur in highly proliferative malignancies or with debulking of extensive tumor burden, is characterized by a group of metabolic disorders caused by the massive and abrupt release of cellular metabolites into the blood after lysis of the malignant cells (Coiffier et al, 2008). The metabolic complications predispose patients with cancer to various clinical complications, including renal failure, seizures, cardiac arrhythmias, and even sudden death. Tumor lysis syndrome occurs primarily during treatment of neoplasms which are rapidly proliferating such as aggressive lymphomas and acute leukemias. It has been reported to occur rarely in solid tumors. With the introduction of more effective therapeutic agents, the possible occurrence of TLS in patients with bulky,

treatment-sensitive solid tumors must be recognized. Therefore, there is a risk of TLS in humans with administration of tarlatamab.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of tarlatamab	• Treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, electrocardiogram (ECG), and clinical laboratory tests
• Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D)	• Dose limiting toxicities (DLTs)
Secondary	
• Evaluate anti-tumor activity of tarlatamab as assessed by additional measures	• Objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • Duration of response (DOR) per RECIST 1.1 • Radiographic progression-free survival (PFS) per Prostate Cancer Working Group 3 (PCWG3) • Overall survival (OS) • Disease Control Rate (DCR) per RECIST 1.1
• Characterize the pharmacokinetics (PK) tarlatamab	• PK parameters for tarlatamab following intravenous (IV) 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 ratio, and half-life ($t_{1/2}$)
Exploratory	
[redacted]	

4. Study Design

4.1 Overall Design

This is an open label phase 1b study evaluating tarlatamab monotherapy.

Tarlatamab will be administered as a short-term IV infusion Q2W (with step dosing) in a 28-day cycle as monotherapy therapy in subjects with de novo or treatment-emergent NEPC.

The study will consist of 2 parts: dose exploration (Part 1) and dose expansion (Part 2).

Dose Exploration (Part 1)

The dose exploration part of the study will enroll up to 20 subjects with relapsed/refractory (RR) NEPC. At the time of initiation of the study, the starting dose will be the highest dose deemed safe and tolerable in the ongoing phase 1 trial of tarlatamab in subjects with small cell lung cancer (Note: based on emerging safety data

from Study 20160323, the starting dose may be lower than the highest dose deemed safe and tolerable). The planned highest dose in this study is not anticipated to exceed the maximum tolerated dose (MTD) as established in the ongoing Study 20160323. Based on results from study 20160323 in small cell lung cancer, the doses that may be explored in this study are presented in Table 4-1.

Due to its known mechanism of action, subjects are at an increased risk for first dose effects (eg, CRS with associated manifestations and any other potentially evolving and unknown first dose effects) following the initial infusion of tarlatamab. To mitigate these risks, a step dosing approach will be implemented. One of the following step dosing approaches will be utilized as the initial dosing schedule based on emerging data and the dosing schedule associated with the highest dose deemed safe and tolerable from the ongoing first-in-human (FIH) study (Note: based on emerging safety data from Study 20160323, the starting dose may be lower than the highest dose deemed safe and tolerable).

- Single-step dosing involving a run-in dose on day 1, followed by a step dose on day 8 (equal to the target dose) and the target dose on day 15 then Q2W.

Based on emerging safety, pharmacokinetic and pharmacodynamic data from this study as well as the ongoing FIH study (20160323) and the recommendations of the DLRT, multiple or parallel dosing cohorts may also be opened simultaneously to assess any of the step-dosing strategies as described above.

Dose exploration will begin with treating 3 to 4 subjects at the Dose Level 1 (dose level 1 is the highest dose deemed safe and tolerable in ongoing phase 1 trial of tarlatamab in subjects with small cell lung cancer [Note: based on emerging safety data from Study 20160323, the starting dose may be lower than the highest dose deemed safe and tolerable]). The study DLT period is 28 days. Once all subjects enrolled at a certain dose level are DLT evaluable, a DLRT will convene. For any dose level, and depending on observed safety data, the following recommendation may occur: 1) dose de-escalation to the next lowest dose level, 2) additional enrollment to the current dose level, 3) dose escalation to the next highest dose level. Dose escalation/de-escalation recommendations will be guided by a modified toxicity probability interval design (mTPI-2) model (Guo et al, 2017) with a target toxicity probability of 0.3 (Table 4-2) and equivalence toxicity interval of (25%, 35%). The operating characteristics in Table 4-3 provide the probability of selecting each dose level and the expected number of treated patients at each dose level for given hypothetical true DLT rates.

Table 4-2. Guideline for Escalation/De-escalation

Number of Evaluable Subjects	Number of DLTs	Decision
3-4	0	E[c]
	1	S
	2	D[b]
	≥ 3	DU
5	0-1	E[c]
	2-3	D[b]
	≥ 4	DU
6	0-1	E[c]
	2	S
	3	D[b]
	≥ 4	DU
7-8	0-1	E[c]
	2	S
	3-4	D[b]
	≥ 5	DU
9	≤ 2	E[c]
	3	S
	4	D[b]

Number of Evaluable Subjects	Number of DLTs	Decision
	≥ 5	DU
10[a]	≤ 2	E[c]
	3	S
	4-5	D[b]
	≥ 6	DU

DLT = dose-limiting toxicity; D = de-escalate to the next lower dose level (can be re-escalated back based on future data); DU = the current dose is unacceptably toxic and can't be re-escalated; E = escalate to the next higher dose; S = stay at the current dose.

[a] As appropriate to better understand safety profile for a dose level, the number of evaluable subjects may be expanded up to 10.

[b] De-escalate guideline applies only when enrollment is allowed to a lower dose level.

[c] If a higher dose level is not allowed, then the current dose level can be expanded.

Table 4-3. Operating Characteristics for mTPI-2 Model

	Dose 1	Dose 2	Early Stopping Probability
Scenario 1			
DLT probability	30%	44%	
Selection probability	67%	20%	13%
Expected # Patients	9	4	
Scenario 2			
DLT probability	13%	30%	
Selection probability	27%	72%	1%
Expected # Patients	7	9	

If late onset adverse events occur 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. The maximum tolerated dose (MTD) will be estimated using isotonic regression (Ji et al, 2010) and the MTD will be the dose level with the estimated DLT rate closest to 0.30. In order to consider a certain dose Level as the MTD at least 6 DLT evaluable subjects must be enrolled at that dose level. No more than 10 DLT evaluable subjects will be enrolled at any specific dose level in dose exploration phase.

Dose exploration phase will end once any of the following events occur:

- Highest planned dose level is determined to be safe and tolerable (minimum of 6 evaluable subjects overall).
- Either Dose Level 1, 2 or 3 is determined to be safe and tolerable (minimum of 6 evaluable subjects) and the next higher dose level is determined to be unsafe and intolerable.

- All planned dose levels (including any intermediate doses or alternate dosing schedules) are determined to be unsafe and intolerable
- DLRT may decide to explore higher dose levels if it is deemed safe and the MTD is not reached at the highest dose planned.
- 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.

The planned highest dose in this study is not anticipated to exceed the MTD as established in the ongoing Study 20160323.

At the time of enrollment, the dose-escalation phase (Part 1) will be eliminated if the recommended phase 2 dose (RP2D) has been selected in the ongoing phase 1 trial of tarlatamab in small cell lung cancer. Tarlatamab will then be dosed based upon the RP2D selected in the phase 1 trial in small cell lung cancer. Note: if Part 1 is initially eliminated based upon the RP2D selection in the phase 1 trial in small cell lung cancer, dose escalation may be opened in the future to explore additional dose(s) and dosing schedule(s) as described above.

Dose Exploration (Part 1)

Due to its known mechanism of action, subjects are at an increased risk for first dose effects (eg, cytokine release syndrome) following the initial infusion of tarlatamab. To mitigate these risks, a step dosing approach will be implemented (involving a run-in dose on cycle 1 day 1 followed by one [redacted] step doses) per the recommendations of the DLRT and based on emerging data from the ongoing phase 1 trial in small cell lung cancer.

Dose Expansion (Part 2)

Once the recommended phase 2 dose (RP2D) has been determined, enrollment will commence in the dose expansion phase to confirm the safety and tolerability of the selected dose and to further evaluate anti-tumor activity.

One or more dosing schedules as described in Part 1 may be pursued in parallel during the expansion phase.

Interim futility analyses (non-binding) will be performed in a continuous manner using Bayesian predictive probability (Lee & Liu, 2008). Interim futility analyses will begin after approximately 20 subjects have been treated and have met the data cutoff criteria defined as a minimum potential follow-up of 9 weeks. Following this initial interim futility analysis subsequent interim futility analyses will be performed after every 10 subjects

have reached the data cutoff criteria, until all subjects are enrolled and evaluated. Further enrollment may be terminated if futility criteria are met in the interim futility analysis.

The interim safety analyses will begin after n=10 dose expansion subjects have had the opportunity to be on treatment for at least 28 days. Following this initial interim safety analysis, subsequent interim safety analyses will be done together with interim futility analyses i.e. after every 10 dose expansion subjects have a minimum potential follow-up of 9 weeks. Based on the interim safety results and reviewing an update estimate of the MTD or RP2D using all available data including data from dose exploration and expansion subjects, the DLRT may modify the dose level of treated subjects. A final estimate of the MTD or RP2D will use all data from dose exploration and dose expansion.

Based on emerging data from the tarlatamab monotherapy in this indication and emerging data from other trials with tarlatamab, the protocol may be amended to include a combination of tarlatamab with anti-PD-1 (L1) agent.

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 60 subjects will be enrolled in the study, with up to 20 subjects to be enrolled in the dose exploration phase (Part 1) and 40 subjects to be enrolled in the dose expansion phase (Part 2). Based on emerging data in Part 2, the protocol may be amended to increase the sample size.

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

4.2.1 Replacement of Subjects

If a subject stops or delays treatment for more than 72 hours for reasons other than DLT during the DLT evaluation period, a replacement subject may be enrolled and assigned to the same dose level.

4.2.2 Number of Sites

Approximately 25 investigative sites in the US, Europe, and Australia 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 selection of the tarlatamab dose and dosing schedule for this study, which includes the number of dose steps (run-in and step doses) will be based on the dose levels that have been deemed safe and tolerable by the DLRT in the ongoing first-in human (Study 20160323). It is anticipated that the selected regimen will demonstrate a comparable safety and tolerability profile to that determined in subjects in SCLC. In addition, the selected regimen is expected to show clinical activity in subjects with NEPC based on the preliminary evidence of efficacy in subjects with SCLC.

Based on Study 20160323, it is expected that the selected regimen will include step dosing (run-in dose on cycle 1 day 1 followed by 1 escalating doses to reach a target dose) during cycle 1, followed by the target dose every 2 weeks thereafter. The step-dosing approach has been implemented to mitigate the risk of cytokine release syndrome. The potential doses of tarlatamab to be used for run-in, step or target doses include mg (or intermediate dose levels), which are under evaluation in Study 20160323.

4.4 End of Study

4.4.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s).

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

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

Amgen will not continue provision of investigational product for subjects after their study participation ends unless it is a legal requirement.

4.4.2 Study Duration for Subjects

The study duration for subjects will be approximately up to 3 years. The study duration will consist of up to 28 days for screening, a variable period on treatment (depending on

the subject's response), and a safety follow-up (SFU) period of up to approximately **60** days (+5 days) after the last dose of tarlatamab. For all subjects who have not withdrawn consent, long-term follow-up assessment will also be conducted every 3 months up to 3 years from the first dose of tarlatamab by clinic visit, telephone or chart review to assess for survival and/or the commencement of subsequent cancer therapy.

4.5 Patient Input on Study Design

Patient input was not obtained 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.

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

103 Metastatic de novo or treatment-emergent neuroendocrine prostate cancer (NEPC) defined as one or more of the following:

- Histological diagnosis of small cell NEPC
- Histologic evidence of prostate cancer with neuroendocrine differentiation as defined by positive immunohistochemical staining for chromogranin and/or synaptophysin in the majority of the tumor sample
- ≥ 2 alterations in Tp53, RB1, and/or PTEN by immunohistochemistry (IHC) or genomic analyses of baseline tumor tissue (by local assessment) or [redacted] (by local assessment). Tp53 by IHC is considered abnormal if ≥ 10% tumor nuclei showed positive staining. RB1 and PTEN by IHC is considered abnormal if ≤ 10% tumor cells showed positive staining. On genomic analyses, nonsynonymous missense or stop-gain mutations, frameshift or non-frameshift indels (insertions and deletions), and/or copy number losses in ≥ 2 of Tp53, RB1, and PTEN is considered abnormal.

104 At least 1 line of prior systemic treatment, including a platinum containing regimen for de novo neuroendocrine prostate cancer (if at the time of NEPC diagnosis they had no prior diagnosis or treatment for prostate carcinoma) or an androgen signaling inhibitor (eg, abiraterone, enzalutamide, darolutamide and/or apalutamide) if treatment-emergent (had a previous diagnosis of prostate carcinoma prior to NEPC diagnosis).

Exception: Subjects may also be included if the aforementioned therapeutic options were medically not appropriate for them.

105 For subjects with treatment-emergent NEPC or de novo NEPC with histologic evidence of prostate cancer with neuroendocrine differentiation as defined by positive immunohistochemical staining for chromogranin and/or synaptophysin in the majority of the tumor sample (unless refractory to prior androgen deprivation treatment), a total serum testosterone of ≤ 50 ng/dl or 1.7 nmol/L

106 Subjects with treatment-emergent NEPC or de novo NEPC with histologic evidence of prostate cancer with neuroendocrine differentiation as defined by positive immunohistochemical staining for chromogranin and/or synaptophysin in the majority of the tumor sample (unless refractory to prior androgen deprivation treatment), without a history of bilateral orchiectomy, are required to remain on luteinizing hormone-releasing hormone (LHRH) analogue therapy during the course of protocol therapy

107 Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 per Prostate Cancer Working Group 3 (PCWG3) modifications (Sections 11.8 and 11.9)

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

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

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

- Definitive treatment was completed at least 2 weeks prior to the first planned dose of study treatment (stereotactic radiosurgery at least 7 days prior to first planned dose of study treatment)
- At least 7 days prior to treatment: any central nervous system (CNS) disease is clinically stable, subject is off steroids for CNS disease (unless steroids are indicated for a reason unrelated to CNS disease), and subject is off or on stable doses of anti-epileptic drugs.

111 Adequate organ function, defined as follows:

Adequate hematological laboratory assessments, as follows:

- Absolute neutrophil count (ANC) $\geq 1 \times 10^9$/L
- Platelet count $\geq 75 \times 10^9$/L
- Hemoglobin ≥ 9 g/dL

Adequate renal laboratory assessments, as follows:

- Estimated glomerular filtration rate based on Modification of Diet in Renal Disease (MDRD) calculation ≥30 mL/min/1.73 m^2

Adequate hepatic laboratory assessments, as follows:

- Aspartate aminotransferase (AST) < 3 x upper limit of normal (ULN) (if liver metastases are present, ≤ 5 x ULN)
- Alanine aminotransferase (ALT) < 3 x ULN (if liver metastases are present, ≤ 5 x ULN)
- Total bilirubin (BIL) < 1.5 x ULN (< 2.0 x ULN for subjects with liver metastases)

Adequate coagulation laboratory assessments, as follows:

- Prothrombin time/international normalized ratio (PT/INR) and partial thromboplastin time (PTT) or activated partial thromboplastin time (APTT) ≤ 1.5 x institutional ULN. Subjects on chronic anticoagulation therapy who do not meet the criteria above may be eligible to enroll after discussion with the medical monitor.

Cardiac function:

- Cardiac ejection fraction ≥ 50%
- No clinically significant electrocardiogram (ECG) findings

5.2 Exclusion Criteria

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

201 History of other malignancy within the past 2 years, with the following exceptions:

- Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated non-muscle invasive urothelial carcinoma

202 History or presence of hematological malignancies unless curatively treated with no evidence of disease ≥ 2 years

203 Untreated (includes new lesions or progression in previously treated lesions) or symptomatic brain metastases and leptomeningeal disease

204 History or presence of relevant CNS pathology such as uncontrolled epilepsy or seizure disorder, aphasia, paresis, dementia, severe brain injuries, Parkinson's disease, cerebellar disease, organic brain disorder, or psychosis

205 Myocardial infarction within 12 months of study day 1, symptomatic congestive heart failure (New York Heart Association > class II), unstable angina, or clinically significant uncontrolled cardiac arrhythmia

206 History of arterial thrombosis (eg, stroke or transient ischemic attack) within 12 months of first dose of tarlatamab

207 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (prednisone dose > 10 mg per day or equivalent dose) or any other form of immunosuppressive therapy within 7 days prior study day 1

208 Active autoimmune disease requiring systemic treatment within the past 2 years **of study day 1** (ie, with the use of disease modifying agents, non-physiologic doses of corticosteroids or immunosuppressive drugs); including current autoimmune sequelae or previous Grade > 2 autoimmune sequelae from checkpoint inhibitors or other immunomodulatory treatments that require systemic therapy

- Exception: Participants with autoimmune endocrine disorders on hormonal supplementation may be enrolled even if > Grade 2 when it first occurred, if approved by the Medical Monitor.

209 Presence of fungal, bacterial, viral, or other infection requiring oral or IV antimicrobials for management within 7 days of first dose tarlatamab.

Note: Simple UTI and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with sponsor. Subjects requiring oral antibiotics who have been afebrile $>$ 24 hours, have no leukocytosis or have any clinical signs of infection are eligible. Subjects who meet these criteria and who were previously on IV antimicrobials should have been off IV antimicrobials for $>$ 48 hours.

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

- Positive Hepatitis B Surface Antigen (HepBsAg) (indicative of chronic Hepatitis B or recent acute hepatitis B).
- Negative HepBsAg and positive for hepatitis B core antibody: hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B.
- Positive Hepatitis C virus antibody: Hepatitis C virus RNA by PCR is necessary. Detectable Hepatitis C virus RNA suggests chronic hepatitis C.

211 Known positive test for human immunodeficiency virus (HIV)

212 Anti-tumor therapy within 28 days of study day 1; concurrent use of hormone deprivation therapy for hormone-refractory prostate is permitted; subjects on a stable bisphosphonate or denosumab for ≥ 30 days prior to study day 1 are eligible

- Exceptions:
  - Subjects who received conventional chemotherapy are eligible if at least 14 days have elapsed and if all treatment-related toxicities have resolved to Grade ≤ 1
  - Prior palliative radiotherapy must have been completed at least 7 days before the first dose of tarlatamab
  - Subjects who received androgen signaling inhibitor (eg, abiraterone, enzalutamide, and/or apalutamide) are eligible if at least 14 days have elapsed and if all treatment-related toxicity has been resolved to Grade ≤ 1

213 Major surgical procedures ≤ 28 days or non–study-related minor procedures ≤ 7 days prior to study day 1. In all cases, the subjects must be sufficiently recovered and stable before treatment administration

214 Currently receiving treatment in another investigational device or drug study, or less than 28 days **from study day 1** since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded with the exception of

[redacted]

215 Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade 1, or to levels dictated in the eligibility criteria with the exception of alopecia or toxicities that are stable and well-controlled and there is agreement to allow by the investigator and sponsor

216 Subject unable to receive both iodinated contrast for CT scans and gadolinium contrast for magnetic resonance imaging (MRI) scans

217 Subject has known sensitivity and immediate hypersensitivity to any components of tarlatamab

218 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's **awareness**

219 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

220 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 **60** days after the last dose of tarlatamab. Refer to Section 11.5 for additional contraceptive information.

221 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for **60** days after the last dose of tarlatamab.

222 Male subjects unwilling to abstain from donating sperm during treatment and for **60** days after the last dose of tarlatamab.

223 Subjects on prior DLL3-targeted therapy may be eligible if discussed with Amgen medical monitor prior to enrollment

224 History of hypophysitis or pituitary dysfunction

225 Has evidence of interstitial lung disease or active, non-infectious pneumonitis.

226 Live and live-attenuated vaccines within 4 weeks prior to study drug administration.

227 History or evidence of SARS-COV2 infection unless agreed upon with Medical Monitor and with no acute symptoms of COVID19 disease within 14 days prior to first dose of IP (counted from day of positive test for asymptomatic subjects).

5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written **external review bodies** approval of the protocol,

informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject or legally authorized representative must personally sign and date the **external review bodies (eg, the institutional review board [IRB]/independent ethics committee[IEC]/regulatory authorities)** 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 at which the subject or legally authorized representative signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned 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 one time at the investigator's decision. Refer to Section 8.1.1.

6. Treatments

Study treatment is defined as any investigational product(s), noninvestigational 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 noninvestigational product**(s)** are referred to as investigational medicinal product and noninvestigational product**(s)/auxiliary**, 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] Tarlatamab
Dosage Formulation	Tarlatamab is supplied as a sterile, single use, preservative free lyophilized drug product containing [redacted] mg of tarlatamab per vial. Tarlatamab is intended for reconstitution with sterile water for injection and dilution in an IV bag with normal saline ([redacted] sodium chloride) and an IV solution stabilizer. The drug product is formulated with L-glutamic acid, sucrose, polysorbate 80, pH [redacted]
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	At the time of initiation of the study, the starting dose will be the highest dose deemed safe and tolerable in the ongoing phase 1 trial of tarlatamab in subjects with small cell lung cancer (Note: based on emerging safety data from Study 20160323, the starting dose may be lower than the highest dose deemed safe and tolerable).
Route of Administration	Tarlatamab will be administered as a short-term IV infusion for 60 minutes followed by a flush once every 2 weeks (with step-dosing).
Accountability	The date, time, package lot number, dose, and the start and stop time of infusion are to be recorded on the individual subject's Investigational Product Administration CRF.
Dosing Instructions	Tarlatamab will be administered at the study center by a qualified staff member. A physician must be available at the time of administration of investigational products. Please refer to IPIM for more details on dosage, administration, and schedule of tarlatamab.

CRF = case report form; IPIM = Investigational Product Instruction Manual; IV = intravenous.
[a] Tarlatamab will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Medical Devices

Investigational medical devices will not be used in this study.

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

Noninvestigational 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.

6.1.3 Noninvestigational Product(s)/Auxiliary Medicinal Product(s)

All **noninvestigational product(s)/auxiliary medicinal product(s)** including, dexamethasone and normal saline, 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 **noninvestigational product(s)/auxiliary medicinal product(s)**. Due to the mechanism of action of tarlatamab, CRS and neurological events are important potential risks. Corticosteroid has been used for prophylaxis and treatment of CRS and neurological events secondary to blinatumomab and other BiTE® molecules.

Prophylaxis with IV hydration 1 L normal saline over 4 to 5 hours immediately following all dose(s) in cycle 1 is required.

Dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) will be administered within 1 hour prior to each dose of tarlatamab in cycle 1.

Dexamethasone dose and schedule may be changed based on emerging safety data.

6.1.4 Other Treatment Procedures

Sites are required to have tocilizumab or siltuximab (if tocilizumab not available) on site for potential treatment of CRS.

6.1.5 Product Complaints

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

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

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

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

The following treatments and/or procedures are excluded within the timeframes specified during the study:

- Other investigational agents
- Concurrent experimental or approved anti-tumor therapies other than study drugs
- Radiation therapy
    - Exception: Radiation therapy for symptom control (eg, bone metastasis) or brain metastases may be allowed after discussion with the Medical Monitor. The radiation therapy should not include the thoracic field and must have been completed at least 7 days before the subsequent dose of tarlatamab
- Chronic systemic corticosteroid therapy (prednisone dose > 10 mg per day or equivalent) or any other immunosuppressive agents with the exception of those required by protocol, treatment for adverse events, CNS metastases, corticosteroid replacement therapy or unless agreed upon by the principal investigator (PI) and Medical Monitor
- Any live vaccine therapies. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed
- Subjects must not schedule any major elective surgery during the treatment period and for at least 30 days after the last administration of study drugs. If a subject undergoes any unexpected surgery during the course of the study, all study treatments must be withheld, and the investigator or designee should notify the sponsor's medical monitor as soon as possible. A subject may be allowed to resume study drugs if both the investigator and sponsor's medical monitor agree to restart study therapy.

6.2 Dose Modification

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

6.2.1.1 Dose Level Review Team

For the dose exploration phase, a DLRT will convene to review the safety data before recommendations to dose escalate. The required DLRT voting members include the Medical Monitor, Global Safety Officer (GSO), and Site Investigator or designee. The DLRT members are responsible for dosing recommendations, which may include

implementing step dosing, escalation to the next dose, de-escalation to a lower dose, exploring intermediate dose levels; continuation, delay or termination of dosing; or repetition or expansion of a cohort; or determination of MTD or RP2D. The DLRT will not make dose escalation recommendations until at least 3 subjects enrolled at the dose level are deemed DLT-evaluable. Cumulative adverse events profile will be taken into consideration when making recommendations on dose escalation or de-escalation. See Section 11.3 for more details regarding the DLRT.

6.2.1.2 Dose-cohort Study Escalation

Details on dose-cohort study escalation and stopping rules will refer to Section 4.1.

6.2.1.2.1 Dose Limiting Toxicity

Dose-limiting toxicity (DLT) is defined as any qualifying toxicity that is at least possibly related to tarlatamab with an onset within the first 28 days following first dose with either of the following criteria:

- Grade 3 adverse event lasting more than 3 days (with the exception of fatigue and Grade 3 non-febrile neutropenia that improves to ≤ Grade 1 within 3 weeks including the use of growth factor support per neutropenia management guidelines [see Section 6.8.6]);
- ≥ Grade 4 adverse event regardless of duration (with the exception of grade 4 non-febrile neutropenia lasting less than or equal to 7 days including the use of growth factor support per neutropenia management guidelines [see Section 6.8.6]).

Laboratory parameters of Grade 4, not considered clinically relevant and improved to Grade ≤ 2 within 72 hours, will not be considered DLT's.

Asymptomatic grade 4 electrolyte abnormalities that last < 72 hours, are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions will not be considered DLTs.

The following adverse events will NOT be adjudicated as DLT regardless of the grade or duration:

- Lymphopenia
- Fever
- Tumor lysis syndrome (TLS) including associated manifestations attributable to TLS (eg, electrolyte abnormalities, renal dysfunction, hyperuricemia)

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

6.2.2.1 Amgen Investigational Product: Tarlatamab

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

6.2.2.1.1 Dosage Adjustment

Subjects should continue on the same target dose of tarlatamab (not including the initial run-in dose and step dose(s)) throughout the study. The two exceptions are subjects who meet criteria for intra-subject dose escalation (see Section 6.2.2.1.4 for more details) and subjects who experienced a DLT or other intolerable tarlatamab-related adverse events but showing evidence of clinical benefit. These subjects will have an option to reduce the dose to the immediate next lower dose level shown to be safe and tolerable in the dose exploration part of the study, after discussion with the Amgen Medical Monitor. The study drug can be resumed once the adverse events recover to Grade 0-1 and the reintroduction of tarlatamab is deemed safe by the investigator, Medical Monitor, and GSO. The subjects must be informed of the risk of continuing on therapy. Each subject is only allowed one dose reduction. For adverse events related to CRS, neurological events, and pituitary dysfunction, please see Sections 6.8.1, 6.8.2, and 6.8.3, respectively for guidelines for dose adjustments.

6.2.2.1.2 Dose Delays

During the first 28 days DLT observation period, if the dosing of tarlatamab is delayed for more than 72 hours for reasons other than DLT during the DLT evaluation period, a replacement subject may be enrolled and assigned to the same dose level. The subject may continue on study only after discussion with the Medical Monitor.

After the 28-day DLT observation period, if the dosing of tarlatamab is delayed for ≤ 2 weeks, the subject should resume the treatment as soon as possible if deemed safe by the investigator. The investigator should inform the Amgen Clinical team as soon as the unexpected dosing interruption occurs. If the dosing of tarlatamab is delayed between 2 to 4 weeks due to severe or life-threatening treatment-related adverse events, the subject can resume treatment if the toxicities resolve to grade ≤ 1 or return to subjects' baseline values within 4 weeks and restarting of therapy has been deemed safe by the investigator and medical monitor.

If the dosing of tarlatamab is delayed for more than 4 weeks due to severe or life-threatening treatment-related adverse events, the subject will be discontinued from investigational product (IP). If the dosing delay occurred under other conditions, the

case will be reviewed by the Sponsor to determine whether and when the subject will be allowed to resume tarlatamab.

For adverse events related to CRS, neurological events, and pituitary dysfunction, please see Sections 6.8.1, 6.8.2, and 6.8.3 respectively for guidelines for dose delays.

6.2.2.1.3 Rules for Withholding or Restarting

Tarlatamab should be withheld for any of the following:

- DLT
- Symptomatic hypophysitis (See Section 6.8.3)
- Criteria for conditional withholding of tarlatamab due to potential hepatotoxicity (Section 6.2.3)

Tarlatamab dosing can be resumed if the toxicities resolve to grade ≤ 1 or return to subjects' baseline values within 4 weeks. The restarting of therapy should be deemed safe by the investigator and medical monitor.

Subjects should not be restarted with tarlatamab if the following treatment-related adverse events occur:

- Any grade ≥ 4 adverse events except those not considered DLT as described in Section 6.2.1.2.2
- Grade 3 adverse event(s) that do not recover to Grade 0-1 within 4 weeks
- Any grade 3 adverse events that recur (with the exception of grade 3 laboratory parameters not considered clinically relevant or recurrent non-febrile grade 3 neutropenia which resolves with supportive care to grade ≤ 1 or returns to subjects' baseline values within 4 weeks)
- Criteria for permanent withholding of tarlatamab due to potential hepatotoxicity (Section 6.2.3)

For adverse events related to CRS, neurological events and pituitary dysfunction, please see Sections 6.8.1, 6.8.2, and 6.8.3 respectively for guidelines for withholding and restarting criteria to pause enrollment.

At any point during the study, enrollment will be paused at the occurrence of 2 or more Grade 4 or one or more Grade 5 IP related adverse events. DLRT will be reconvened to review the safety data and determine appropriate next step that may include but not limited to implementing safety/toxicity management, informing health authorities, voluntarily putting the clinical trial on hold, or proceeding with enrollment (note: following the occurrence of an enrollment pause and DLRT review, a subsequent enrollment pause will occur at the occurrence of 2 or more new Grade 4 or one or more Grade 5 IP

related adverse events; additionally, if a pause and a DLRT has already occurred and the appropriate safety/toxicity management for Grade 4 adverse events have already been implemented a subsequent enrollment pause may not occur).

6.2.2.1.4 Intra-subject Dose Escalation

In Part 1, certain subjects who enroll in the study and receive the full planned dose for at least 2 cycles will be allowed to receive a higher dose of tarlatamab once such dose is deemed safe by DLRT. Both the medical monitor and PI must deem it safe before a subject is considered for intra-subject dose escalation. The subject must be informed of the potential risks and benefits. Intra-subject dose escalation should only occur if the subject experienced ≤ Grade 1 toxicity during the previous course. If any cases of Grade ≥ 3 toxicity occur at the current or any previous lower dose levels, no intra-patient dose escalation should be allowed at that dose level. See Section 8.1.2 for more details on the changes regarding the schedule of activities for subjects who undergo intra-subject dose escalation.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

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

6.3 Preparation/Handling/Storage/Accountability

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

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

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

6.4.2 Blinding

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

6.5 Treatment Compliance

Compliance with treatment and the corresponding assessments should be followed according to the Schedule of Activities (Section 1.3) and the Treatment Procedures (Section 8.2). Refer to the IPIM for additional information.

6.6 Treatment of Overdose

The effects of overdose of this product are not known. **The administered investigational product 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 as per Section 11.4.

A dose of > 10% higher than the intended investigational product dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" (See Section 11.4).

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior therapies that were being taken/used from 1 month prior to signing informed consent will be collected. For all prior therapies not taken for prostate cancer, collect therapy name, indication, dose, unit, frequency, route, start and stop dates.

For all prior therapies taken for prostate cancer (eg, chemotherapy or hormonal therapy), 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 (biochemical [ie, a rising [redacted] radiographic, and/or symptomatic)
- response (resistant versus sensitive): categorized on the basis of the post-therapy [redacted] or radiographic change pattern for agents that reduce tumor burden

NOTE: A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane.

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). Details of prior radioisotope therapy should also be recorded.

6.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary, including the use of growth factors such as erythropoiesis-stimulating proteins as well as granulocyte colony stimulating factor (G-CSF), to provide adequate supportive care except for those listed in Section 6.1.6.

Concomitant therapies are to be collected from signing of the informed consent through the end of SFU period. For concomitant therapies being taken for the disease under study (eg, steroids, chemotherapy), collect therapy name, dose, unit, frequency, start date and stop date. For all other concomitant therapies, including vaccines collect therapy name, indication, dose, unit, frequency, route, start date and stop date, and record in the electronic case report form (eCRF).

6.7.3 Vaccines

Every effort should be made to fully vaccinate patients prior to 14 days from first dose of IP. The use of vaccines except live and live-attenuated vaccines will be allowed during therapy per regional and institutional standard of care. However, SARS-COV2 vaccinations should be avoided during screening (within a minimum of 14 days from first dose of IP) and should be also avoided in the first treatment cycle for better assessment of safety parameters. Throughout the trial, SARS-COV2 vaccination should be avoided within 3 days after the administration of IP. In the event where a patient requires steroids for treatment of AEs, vaccination should be avoided while on steroids. **Live and live attenuated vaccines can be used at least 60 days after the last dose of tarlatamab.**

6.8 Support Care and Potential Risk Management Guidelines for Tarlatamab

6.8.1 Cytokine Release Syndrome (CRS)

CRS is clinically defined and may have various manifestations. There are no established diagnostic criteria. Signs and symptoms of CRS may include (Lee et al, 2014):

- **Constitutional:** fever ± rigors, fatigue, malaise, myalgias**,** anorexia, arthralgias, nausea, vomiting, headache

- **Neurologic:** headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures
- **Respiratory:** dyspnea, tachypnea, hypoxemia
- **Cardiovascular:** tachycardia, hypotension, widened pulse pressure, increased cardiac output (early), potentially diminished cardiac output (late)
- **Gastrointestinal:** nausea, vomiting, diarrhea
- **Renal:** azotemia
- **Hepatic:** transaminitis, hyperbilirubinemia
- **Hematology/Coagulation:** hypofibrinogenemia ± bleeding, elevated D-dimer
- **Skin:** rash

CRS is an identified risk of tarlatamab administration. Subjects may be at an increased risk for CRS during the first few days following the initial infusion of tarlatamab and after a dose step increase. CRS may be life-threatening or fatal. Infusion reactions may be clinically indistinguishable from manifestations of CRS. Subjects will be hospitalized for intensive monitoring for 48 hours post tarlatamab infusion during all cycle 1 doses (refer to Section 8.1.2 for hospitalization guidance). Throughout the infusion with tarlatamab and at least 4 hours after the end of infusion, monitor subjects intensively for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to CRS.

Grading and management of CRS should be performed according to the guidelines provided in Table 6-2 (Lee et al, 2014). For subjects with suspected CRS, samples may be collected for analysis after discussion with the Medical Monitor.

Table 6-2. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity [a]	Minimum Expected Intervention	Instructions for Dose Modifications of Tarlatamab
1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise	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
2	Symptoms require and respond to moderate intervention • Oxygen requirement <40%, OR • Hypotension responsive to fluids or low dose of one vasopressor, OR Grade 2 organ toxicity or grade 3 transaminitis per CTCAE criteria	Administer: • Symptomatic treatment (eg, paracetamol/ acetaminophen for fever) • Supplemental oxygen when oxygen saturation is < 90% on room air • Intravenous fluids or low dose vasopressor for hypotension when systolic blood pressure is < 85 mmHg. Persistent tachycardia (eg >120 bpm) may also indicate the need for intervention for hypotension. Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution to CRS grade ≤ 1, whichever is earlier. For subjects with extensive co-morbidities or poor performance status or if CRS does not resolve to grade ≤ 1 in 48 hours, manage per grade 3 CRS guidance below.	If CRS occurs during tarlatamab treatment, immediately interrupt the infusion and delay the next tarlatamab dose until the event resolves to CRS grade ≤ 1 for no less than 72 hours. Resume tarlatamab at same dose or reduce to next lower dose, if clinically indicated (continuation with the next planned dose may be allowed after discussion with the Amgen Medical Monitor). Permanently discontinue tarlatamab if there is no improvement to CRS ≤ grade 1 within 7 days.

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Footnotes defined on last page of table

Table 6-2. Grading and Management of Cytokine Release Syndrome (CRS)

CRS Grade	Description of Severity [a]	Minimum Expected Intervention	Instructions for Dose Modifications of Tarlatamab
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	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. Investigators should consider use of tocilizumab[c,d] 8 mg/kg over 1 hour (not to exceed 800 mg). Repeat tocilizumab[c,d] every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Maximum of 3 doses in a 24-hour period. Maximum total of 4 doses. If tocilizumab is not available, siltuximab (an anti-IL-6 monoclonal antibody) may be used. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an intravenous infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (Sylvant Prescribing Information), and the CARTOX Working Group Guidelines for CRS management (Neelapu et al, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of tarlatamab. Siltuximab may not be repeated in an individual subject who develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab. Investigators may also consider additional therapy, based on clinical judgment.	If CRS occurs during tarlatamab treatment, immediately interrupt tarlatamab and delay the next dose until event resolves to CRS grade ≤ 1 for no less than 72 hours. Resume tarlatamab to next lower dose (continuation at same dose with dexamethasone premedication may be allowed after discussion with the medical monitor). Permanently discontinue tarlatamab if there is no improvement to CRS ≤ grade 2 within 5 days or CRS ≤ grade 1 within 7 days. Permanently discontinue tarlatamab or reduce to the next lower dose if CRS grade 3 occurs at the initial run in dose (ie, at MTD1) (applicable only after MTD1 has been defined).

CRS Grade	Description of Severity [a]	Minimum Expected Intervention	Instructions for Dose Modifications of Tarlatamab
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 steroid use should be discussed with the Amgen medical monitor. Investigators should consider use of tocilizumab[c,d] 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab[c,d] every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Maximum of 3 doses in a 24-hour period. Maximum total of 4 doses. If tocilizumab is not available, siltuximab (an anti-IL-6 monoclonal antibody) may be used. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an intravenous infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (Sylvant Prescribing Information), and the CARTOX Working Group Guidelines for CRS management (Neelapu et al, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of tarlatamab. Siltuximab may not be repeated in an individual subject who develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab. Investigators may also consider additional therapy, based on clinical judgment.	If CRS occurs during tarlatamab treatment, immediately stop the infusion. Permanently discontinue tarlatamab therapy.

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[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] If tocilizumab is not available, siltuximab (an anti-interleukin-6 [IL-6] monoclonal antibody) may be used in the management of cytokine release syndrome, following the criteria outlined in the Management of Adverse Events table. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an intravenous infusion, consistent with the prescribing information for the treatment of multicentric

Castleman's disease (Sylvant Prescribing Information), and the CARTOX Working Group Guidelines for CRS management (Neelapu, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of tarlatamab. Siltuximab may not be repeated in an individual subject that develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab.

[d] A subgroup analysis for subjects treated with siltuximab will be evaluated, including CRS outcomes, safety, and PK data.

Re-start of treatment after CRS:

After a grade 2 or 3 CRS event, the next infusion may be administered if all of the following criteria are met:

- The Amgen medical monitor must be consulted prior to re-starting treatment
- If CRS occurred during tarlatamab infusion, infusion has been interrupted for at least 72 hours
- The event has resolved to grade ≤ 1 prior to re-starting treatment

If a subject experiences two separate grade 3 CRS events, tarlatamab must be permanently discontinued.

6.8.2 Neurologic Events

Please see Table 6-3 for the management of adverse events related to neurological events. For subjects with suspected neurological events, samples may be collected for analysis after discussion with the Medical Monitor.

Table 6-3. Management of Adverse Events Related to Neurologic Events

Toxicity	Grade*	Instructions for Treatment Interruption and Restart
Neurologic Events	3**	• Interrupt tarlatamab until the event improves to grade ≤ 1 and administer corticosteroids per local practice • Resume tarlatamab no less than 72 hours after the initial observation of the grade 3 adverse event at one dose level below • Permanently discontinue if: o Initial grade 3 neurologic event does not improve to grade ≤ 1 within 7 days, OR o Grade 3 neurologic event reoccurs at the lower dose level within 7 days of re-initiation
	4	• Permanently discontinue tarlatamab
	Seizure	• Interrupt tarlatamab, administer corticosteroids and anti-seizure medication per local practice • For restart, refer to grade 3 neurologic events above for dose level rules for re-instituting infusion. • Do not re-initiate tarlatamab until 7 days after the last seizure and after therapeutic levels of anti-seizure medication are likely to have been achieved. • Permanently discontinue if a second seizure occurs with re-initiation of tarlatamab at any dose

* Per CTCAE Guidelines Version 4.0
** For adverse events Grade ≤ 2, please follow institutional guidelines for management.

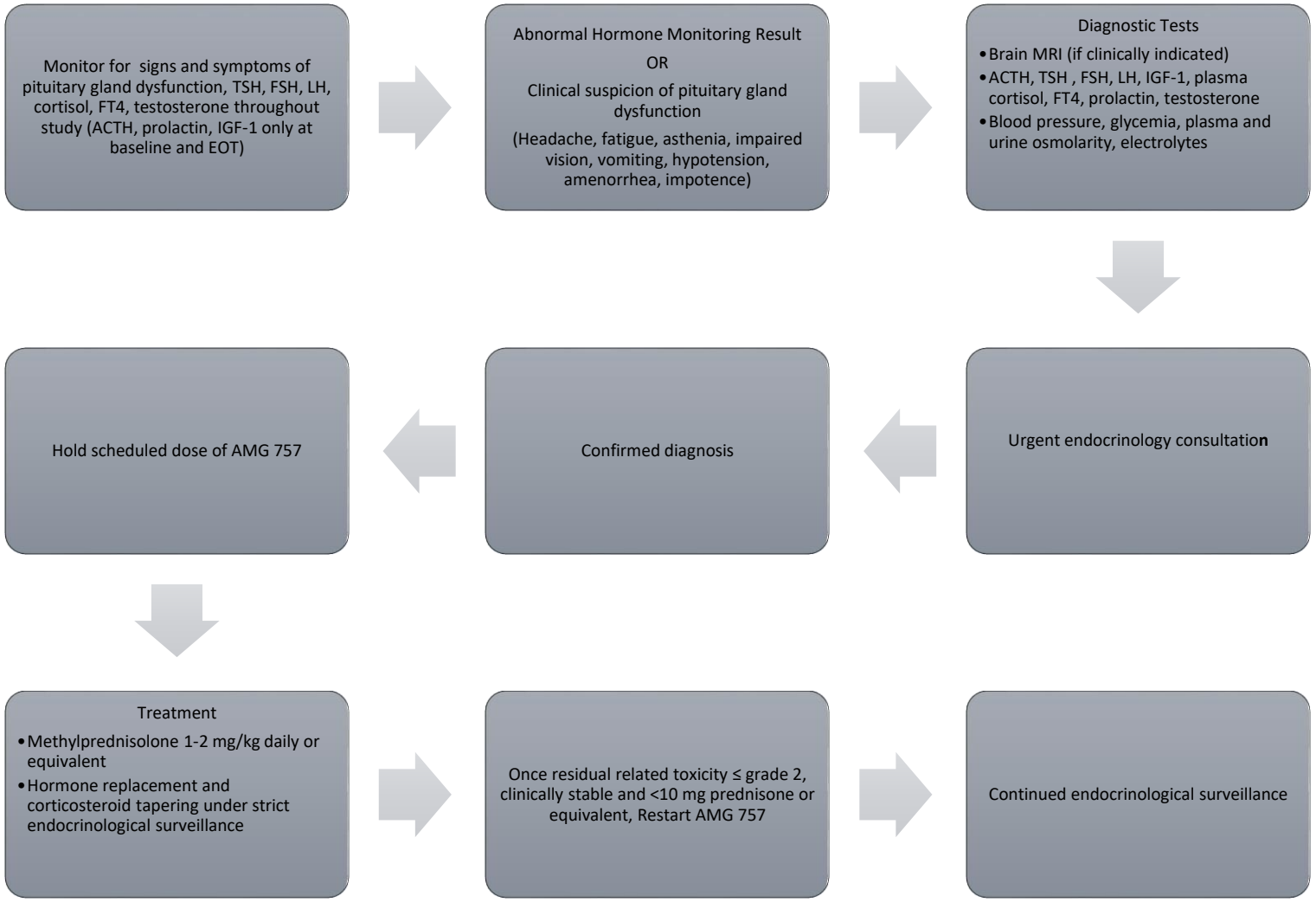
6.8.3 Pituitary Dysfunction

Based on the expression of DLL3 in the pituitary and observations in the cynomolgus monkey toxicology studies, there is a key risk of pituitary dysfunction in humans with administration of tarlatamab.

Early recognition of signs and symptoms and prompt intervention are essential. Symptoms may derive from hormonal deficiencies and by the mass effect due to the swelling of the gland. The most common presentation includes headaches, asthenia, fatigue, nausea, weakness, lethargy, erectile dysfunction, and loss of libido.

The diagnosis and management of pituitary gland dysfunction should be performed according to the guidelines provided in Figure 6-1. Cortisol, thyroid stimulating hormone (TSH), free thyroxine (FT4), follicle stimulating hormone/luteinizing hormone (FSH/LH), and testosterone will be evaluated at baseline and monitored throughout the study. Adrenocorticotropic hormone (ACTH), prolactin, and insulin-like growth factor 1 (IGF-1) will also be evaluated only at baseline and at the end of therapy. If any indications of pituitary gland dysfunction arise, a complete set of pituitary hormone panel will be evaluated, an endocrinologist will be consulted, and an MRI of the brain/pituitary will be conducted. After a confirmed diagnosis, tarlatamab will be withheld and corticosteroids and hormone replacement administered if clinically indicated. Please see Figure 6-1 for guidelines for restarting tarlatamab. This management recommendation may be revised based on emerging clinical data.

Figure 6-1. Monitoring and Management of Pituitary Gland Dysfunction (Gonzalez et al, 2016)



6.8.4 Covid-19 Management

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
SARS CoV2 infection and COVID19 disease				
asymptomatic	Interruption required until at least 10 days since positive SARS-COV-2 test UNLESS patient previously fully vaccinated against SARS-COV-2. If patient previously vaccinated and tests positive, then discuss with Medical Monitor.	Follow local guidelines and standard of care for COVID-19 treatment and isolation Contact Amgen Medical Monitor within 1 business day to ensure appropriate documentation & management of study activities	• Re-start possible upon agreement between Investigator and Amgen Medical Monitor provided: ○ There are no new findings on physical exam related to SARS-COV-2, AND ○ Subject tests negative for SARS-COV-2 by RT-PCR ○ Consider CT of the chest imaging & EKG, ECHO and cardiology assessment prior to re-start of IP. OR If subject continues to test positive for SARS-COV-2 more than 10 days after initial positive test, or if subject initially tests positive in the setting of prior COVID vaccination, resume IP only after discussion with patient and reassessment of individual risk/benefit & perform Ct of chest imaging & EKG (required) prior to re-start of IP. Consider ECHO and cardiology assessment • Consider hospitalization for re-start of IP based on length of treatment interruption, risk of CRS at restart, and amount of time since patient was last treated • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated	Immediately stop the infusion (if applicable) and permanently discontinue IP therapy IF: Subject required treatment interruption greater than 28 days and upon discussion with Amgen Medical Monitor the decision is made to permanently discontinue treatment OR Initial benefit/risk assessment for individual patient is not maintained any longer

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

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
SARS CoV2 infection and COVID19 disease				
			• Premedication and assessments: follow guidance in SOA tables	

6.8.5 Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome, a preventable complication of cancer therapies, is a result of rapid tumor necrosis with release of intracellular ions into the bloodstream. It is characterized by hyperuricemia, hyperkalemia, and hyperphosphatemia. TLS occurs primarily in hematological malignancies and high-grade lymphomas. The occurrence of TLS in solid tumors is rare but is more common in highly responsive tumors with large tumor burdens. Pretreatment elevation of serum lactate dehydrogenase (LDH) and uric acid, and pre-existing renal failure are risk factors for the development of TLS (Kallab and Jillella, 2001). In light of the extremely low incidence of TLS in patients with solid tumors, routine prophylactic measures, such as allopurinol and alkaline hydration, cannot be recommended in all patients. However, the potential for TLS in patients with large tumor burdens who present with renal insufficiency, dehydration, hyperuricemia, and elevated serum LDH levels must be recognized, to allow for appropriate monitoring after treatment and early initiation of therapeutic measures if necessary (Kalemkerian et al, 1997). Prophylaxis with IV hydration 1 L normal saline over 4 to 5 hours immediately following all dose(s) in cycle 1 is required. Careful monitoring of fluid status and additional IV hydration as clinically appropriate is recommended. Allopurinol or rasburicase can be considered for both prophylaxis and/or treatment of hyperuricemia.

6.8.6 Neutropenia

Neutropenia has been observed in patients receiving tarlatamab. The risk mitigation plan includes monitoring of laboratory parameters (including, but not limited to, white blood cell count and absolute neutrophil count) which will be evaluated at baseline and monitored throughout the study. Specific recommendations for the management of neutropenia, and infusion interruption and stopping rules are found in the Table 6-4.

Table 6-4. Tarlatamab Dose Modification Guidelines for Adverse Events

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Non-febrile Neutropenia				
3	Interrupt tarlatamab until the event improves to grade ≤ 2	Assess for other potential etiologies of neutropenia, including concomitant medications and underlying infection Consider bone marrow biopsy, anti-neutrophil antibodies Granulocyte colony-stimulating factor (G-CSF) administration permitted	Resume tarlatamab no less than 72 hours after the initial observation of the grade 3 adverse event at the same dose level	Initial grade 3 non-febrile neutropenia does not improve to ≤ grade 1 in 3 weeks
4	Interrupt tarlatamab until the event improves to grade ≤ 2	Assess for other potential etiologies of neutropenia, including concomitant medications and underlying infection Consider bone marrow biopsy, anti-neutrophil antibodies Consider G-CSF administration	Resume tarlatamab no less than 72 hours after the initial observation of the grade 4 adverse event and discuss with medical monitor the restarting dose	Initial grade 4 non-febrile neutropenia event lasts > 7 days

G-CSF = granulocyte colony-stimulating factor

7. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or **noninvestigational product(s)/auxiliary medicinal product(s)**, 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 **noninvestigational product(s)/auxiliary medicinal product(s)**, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 7.1, 7.2.1, and 7.2.2.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or **noninvestigational product(s)/auxiliary medicinal product(s)** 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 **noninvestigational product(s)/auxiliary medicinal product(s)** and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 1.3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or **noninvestigational product(s)/auxiliary medicinal product(s)** 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 **noninvestigational product(s)/auxiliary medicinal product(s)** 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 (if applicable, refer to Table 6-3)
- subject request
- ineligibility determined
- protocol deviation
- non-compliance
- no longer clinically benefitting (may include clinical deterioration [disease or therapy related] or need for a change in systemic therapy; Scher et al, 2016)
- requirement for alternative therapy

7.2 Discontinuation From the Study

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

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

Not applicable for this study.

7.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

7.3 Lost to Follow-up

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

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

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

8. Study Assessments and Procedures

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

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

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

8.1 General Study Periods

8.1.1 Screening and Enrollment

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject or legally authorized representative has signed the ICF, the site will register the subject and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days.

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

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time.

Rescreen subjects must first be registered as screen failures and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 28 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Treatment begins on cycle 1 day 1 when the first IV infusion of investigational product is administered to a subject. The study procedures to be completed during the treatment period are designated in the Schedule of Activities (Section 1.3).

The results of the cycle 1 day 1 laboratory tests must be available before starting treatment with tarlatamab. Laboratory assessments that were done within 24 hours prior to infusion do not need to be repeated, except for cycle 1 day 1 dosing where laboratory assessments should be collected within 4 hours before cycle 1 day 1 dosing of tarlatamab. Clinical evaluation should be completed within 6 hours prior to the first dose of tarlatamab.

All assessments and procedures should be collected at the exact nominal time point as noted in the Schedule of Activities. If unable to perform a procedure at the specified nominal time point, collect it as close as possible to the nominal time point and record the actual collection time.

The EOT visit will occur at the end of the last treatment cycle. For subjects who prematurely discontinue IP treatment, the EOT visit should occur as soon as possible after the last dose of investigational product was administered.

Hospitalization Guidance

All subjects will be hospitalized for intensive monitoring for 48 hours post tarlatamab infusion during all cycle 1 doses. Hospitalization is not required for cycle 2 unless a subject experiences grade 2 or higher CRS or neurological events in cycle 1 (minimum of 24 hours hospitalization required post tarlatamab infusion on C2D1 if grade 2 or higher CRS or neurological events are noted in cycle 1). The subjects may be

discharged after this period if there are no signs and symptoms of cytokine release syndrome or other acute toxicities.

Study sites must have immediate access to a medical intensive care unit staffed by critical care providers.

If subjects are not hospitalized during cycle 2, subjects will be observed for 8 hours post tarlatamab infusion.

8.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason to further assess the risk of delayed adverse events, an SFU visit will be performed approximately **60** (+5) days after the end of the last dose of tarlatamab.

The study procedures to be completed during the SFU period are designated in the Schedule of Activities (Table 1-2).

The following procedures will be completed for patients who have not started subsequent anti-cancer therapy. Additional tests can be conducted at the discretion of the investigator.

- Clinical evaluation
  - Physical examination as per standard of care (including medical/surgical history). Physical examination findings should be recorded on the appropriate eCRF.
  - ECOG performance status
  - Weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry
- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant and rescue medications

This information may be collected by clinic visit, telephone or chart review.

8.1.4 Long-term Follow-up

Long-term follow up will be conducted every 3 months up to 3 years from the first dose of tarlatamab 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 only.

For subjects who discontinued treatment for any reason other than confirmed progressive disease, every effort should be made to perform radiographic imaging (CT/MRI/bone) of the chest, abdomen, pelvis, bone, and all other known sites of disease every 3 months until documentation of confirmed disease progression per PCWG3 guidelines (Sections 11.8 and 11.9), clinical progression, start of new anticancer therapy, or up to 3 years after the first dose of tarlatamab, whichever occurs first.

8.2 Description of General Study Assessments and Procedures

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

8.2.1 General Assessments

8.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the **external review body** 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 **investigational product(s)**.

8.2.1.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started prior to enrollment through the time of consent. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history eCRF.

Relevant medical history, including antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding and infection (resolved and ongoing) will be collected. The current toxicity grade will be collected for each condition that has not resolved. Any unresolved medical history will be graded according to Common Toxicology Criteria for Adverse Events (CTCAE) version 4.0 (Section 11.4) unless specified otherwise.

All prior cancer treatment therapies will be collected.

8.2.1.4 Physical Examination

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

8.2.1.5 Physical Measurements

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

8.2.1.6 Performance Status

ECOG performance status (Section 11.10) assessments will occur at time points specified in the Schedule of Activities (Section 1.3).

8.2.1.7 Neurological Examination

A neurological examination will be performed as outlined in the Schedule of Activities (Section 1.3). 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 eCRF. Abnormal findings found after the subject is dosed will be reported on the Event page of the eCRF.

A more detailed neurological assessment may be performed in subjects at selected sites.

8.2.1.8 Writing Test

Subjects will be asked to provide writing tests in order to detect early cerebellar signs as outlined in the Schedule of Activities (Section 1.3). Subjects will write down the current date, location of the clinic, and the current time in a sentence. The sentence format should be repeated each time throughout the study. Interpretation of writing sample results will be based solely on the investigator's assessment.

8.2.1.9 Mini-Mental Status Examination

The Mini Mental Status Examination (MMSE) Version 2 will be performed as part of the Clinical Evaluation as outlined in the Schedule of Activities (Section 1.3). The MMSE is a 30-point healthcare professional administered questionnaire to assess potential

subjects for cognitive impairment. The assessment covers eight categories, such as orientation to time, orientation to place or language, with a total score that ranges from 0 to 30 (30 indicates the best possible outcome). The overall total score should be recorded on the appropriate eCRFs.

8.2.2 Efficacy Assessments

8.2.2.1 Radiologic Imaging Assessment

Radiographic assessments will be obtained as scheduled in Section 1.3 irrespective of cycle duration including dose delays and treatment discontinuation.

For subjects developing COVID19 during screening period following screening imaging, consider repeating CT of chest imaging following resolution.

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 the chest, abdomen, and pelvis, all other known sites of disease and magnetic resonance imaging (MRI) of the brain if a subject has signs or symptoms suggestive of CNS metastases. The MRI/CT can be obtained earlier if clinical deterioration necessitates an earlier scan at the discretion of the managing physician. The same contrast and modality used at screening should be used for all subsequent assessments. ^{99m}Tc-MDP (^{99m}technetium methylene diphosphonate) bone scan is required for each radiologic imaging and tumor assessment.

Tumor burden assessments will be performed per PCWG3 guidelines (Sections 11.8 and 11.9). To confirm soft tissue disease progression, a second MRI/CT scan must be performed at least 4 weeks after the first detection of soft tissue disease 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 response as measured by RECIST 1.1. Planar bone scintigraphy must be performed using

conventional ^{99m}technetium methylene diphosphonate radionuclide (^{99m}Tc-MDP) or other equivalent ^{99m}Tc-labeled radiotracers. Confirmation of bone disease progression by bone scan should be performed per PCWG3 guidelines. Disease progression based on both MRI/CT and bone scans will be used in radiographic progression endpoints (eg, radiographic PFS) evaluation. Soft-tissue progression based on MRI/CT scan will be used in response endpoints (eg, objective response and DOR) evaluation. Treatment beyond confirmed tumor progression may be allowed as per PCWG3 guidelines (Section 11.8; Scher et al, 2016). 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 (Section 1.3).

8.2.3.1 Vital Signs

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

8.2.3.2 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: Heart Rate, QRS, QT, QTc, and PR intervals. The PI or designated site physician will review all ECGs. 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.

8.2.3.3 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent

and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

8.2.3.4 Other Safety

8.2.3.4.1 Echocardiogram (ECHO)/Multigated Acquisition (MUGA) Scan

Echocardiogram (ECHO) or multigated acquisition (MUGA) will be performed to assess cardiac ejection fraction and will occur at time points specified in the Schedule of Activities (Section 1.3). ECHO/MUGA should include an evaluation from left ventricular ejection fraction (LVEF). Additional ECHO/MUGA assessments may be performed as clinically indicated.

For subjects developing COVID19 during screening period following screening ECHO assessments, consider repeating ECHO following resolution.

8.2.3.4.2 Hypersensitivity

Hypersensitivity reactions have been reported in patients treated with tarlatamab including rare severe events. Clinical signs and symptoms of hypersensitivity may include but are not limited to rash and bronchospasm. Monitor patients for signs and symptoms of hypersensitivity during treatment with tarlatamab and manage as clinically indicated. Withhold or consider permanent discontinuation of tarlatamab based on severity.

8.2.4 Adverse Events and Serious Adverse Events

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

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

8.2.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE and is described in Section 11.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the **safety follow-up visit or 60 days after the last day of the dosing interval of investigational product(s) or noninvestigational product(s)/auxiliary medicinal product(s), whichever is later,** 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 safety follow-up visit or 60 days after the last day of the dosing interval of investigational product(s) or noninvestigational product(s)/auxiliary medicinal product(s), whichever is later** are reported using the Events CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee **immediately and no later than** 24 hours of the investigator's awareness of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor **immediately and no later than** 24 hours of it being available.

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

8.2.4.1.3 Serious Adverse Events After the Protocol-required Reporting Period

During the long-term follow-up period, if the investigator becomes aware of serious adverse events suspected to be related to investigational product after the protocol-required reporting period (as defined in Section 8.2.4.1.2) is completed, then these serious adverse events will be reported to Amgen **immediately and no later than** 24 hours following the investigator's awareness of the event on the Events CRF.

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

Serious adverse events reported **after the end** of the **study** will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product. If further safety related data is needed to fulfill any regulatory

reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subjects ends the study.

8.2.4.2 Method of Detecting Adverse Events and Serious Adverse Events

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

8.2.4.3 Follow-up of Adverse Events and Serious Adverse Events

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

All new information for previously reported serious adverse events must be sent to Amgen **immediately and no later than** 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 **investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s)** 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 holding the relevant Investigational New Drug/Clinical Trial Application for either tarlatamab or [redacted] has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of tarlatamab or [redacted] under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, **external review body**, and investigators.

Individual safety reports for suspected unexpected serious adverse reactions **will be reported by the sponsor** according to local regulatory requirements **(eg, electronic**

submission to the Eudravigilance database in the EU as per EU Clinical Trial Regulation 536/2014) as well as 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 IB and will notify the **external review body**, if appropriate according to local requirements.

Amgen will prepare a single Development Safety Update Report (also referred to as Annual Safety Report in the European Union) for the Amgen Investigational Product. To ensure that consolidated safety information for the study is provided, this single Development Safety Update Report will also include appropriate information on any other investigational products used in the clinical study, if applicable.

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 Other Safety Findings/Special Situations

All medication errors, misuse or abuse of the investigational product when associated with a serious adverse event must be reported to Amgen or designee immediately and no later than 24 hours of the investigator's awareness by collecting and recording the Other Safety Findings (OSF)/Special Situations (SS) event on the Clinical Trial electronic Serious Adverse Event (eSAE) Contingency Report Form and submitting the form to Amgen Global Patient Safety or designee.

Further details and definitions regarding OSF/SS - medication errors, misuse, or abuse, can be found in Section 11.4.

8.2.4.7 Pregnancy

Details of all pregnancies in female partners of male subjects will be collected after the start of study treatment and until **60** days after last dose of investigational product **and/or noninvestigational product(s)/auxiliary medicinal product(s)**.

If a pregnancy is reported, the investigator is to inform Amgen **immediately and no later than** 24 hours of learning of the pregnancy 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 are provided in Section 11.5.

8.2.5 Clinical Laboratory Assessments

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

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event**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 (Section 1.3).

8.2.6 Pharmacokinetic Assessments

All subjects enrolled will have PK samples assessed.

Blood samples will be obtained for determination of serum concentrations of tarlatamab at the time points specified in the Schedule of Activities (Section 1.3). Blood must not be drawn from a port catheter during IP infusion and must wait 5 minutes after end of infusion prior to PK sample collection. If a permanent central line with more than one lumen is used, blood draws can be done via the lumen that is not used for drug administration. However, the preference is for PK samples to be drawn peripherally. 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 in the eCRF.

Concentrations of tarlatamab will be measured from collected PK samples on an ongoing cohort-by-cohort basis. Cumulative data from any preliminary PK analyses will be made available at the time of dose level review meetings (DLRMs).

Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

8.2.7 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. [redacted]

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

[redacted]

8.2.9 Biomarkers

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

8.2.9.1 Biomarker Assessment During the Study

[redacted]

8.2.9.2 Biomarker Discovery

[redacted]

[redacted]

8.2.9.2.1 Biomarker Development/Future Research

Biomarker Development refers to using samples collected for Biomarker Discovery for future research after the study ends. 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 **noninvestigational product(s)/auxiliary medicinal product(s)**.

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 tarlatamab.

9. Statistical Considerations

9.1 Statistical Hypotheses

No statistical hypotheses will be tested.

9.2 Sample Size Determination

The sample size in the dose exploration 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 dose level, 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 dose level, there is 34% to 80% probability. With 6 subjects in a dose level, there is a 47% to 91% probability of observing at least 1 DLT if the true DLT rate is 10% to 33% and with 10 subjects in a dose level, there is a 65% to 98% probability.

In the dose expansion phase, a subject number of 40 will provide an 87% probability of observing at least 1 adverse event with 5% incidence rate. With the 40 subjects and 20% overall response rate, the expected 95% CI would be 9% to 36%.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

The Safety Analysis Set will consist of all subjects who receive at least 1 dose of tarlatamab. The analysis of all safety and efficacy endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set.

For Part 1 of the study, 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 tarlatamab with an evaluable DLT endpoint. The DLT endpoint is evaluable if either: 1) the subject experiences a DLT, or 2) the subject does not experience a DLT and receives IP treatment as planned in cycle 1 and has been followed for safety events a minimum of 28 days from start of treatment

The Interim Efficacy Analysis Set will contain all subjects in the Safety Analysis Set who have had the opportunity to be followed for at least 9 weeks starting from day 1. Subjects who stopped disease assessments prior to 9 weeks will be included in this analysis set if the data cutoff is at least 9 weeks after their first dose date. Interim efficacy analysis will be performed on this Interim Efficacy Analysis Set.

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

9.3.2 Covariates

The relationship between covariates and efficacy endpoints may be explored if appropriate.

9.3.3 Subgroups

Subgroups will be prespecified in the statistical analysis plan.

9.3.4 Handling of Missing and Incomplete Data

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

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 4.4.1.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. During dose exploration and formally during DLRMs, Amgen, in consultation with the site investigators, will review all available cumulative data by dose level prior to making dose escalation or dose de-escalation recommendations. 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, Amgen will conduct evaluations of the grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible early trial termination has been reached. If this threshold is met, enrollment to dose expansion will be halted pending review of safety data by the DLRT. After receiving the DLRT recommendation, Amgen will choose to take one of the following actions.

1) Terminate the trial

2) Resume Dose Exploration with a schedule as outlined in the protocol and recommended by the DLRT.

3) Amend the protocol to potentially improve the benefit/risk for subjects (eg, increase safety monitoring, modify dose/schedule, mandate premedication).

4) Continue dose expansion without any changes.

The stopping rules use a Bayesian approach proposed by Thall and colleagues (Thall et al, 1995) to terminate the study if the posterior probability that the grade 4 or higher treatment-related adverse event rate of 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%.

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 Subjects if Observing This Many Grade 4 or Higher Treatment-related Adverse Events
10	≥ 4
20	≥ 6
30	≥ 9
40	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%	39.5
0.15	9.7%	37.6
0.20	25.8%	33.9
0.25	47.7%	28.8
0.30	69.2%	23.4

Interim futility analyses (non-binding) will be performed in a continuous manner using Bayesian predictive probability (Lee & Liu, 2008). Interim futility analyses in Part 2 will begin after approximately 20 subjects have been treated and has a minimum potential follow-up of 9 weeks. Interim futility analyses will be based on the ORR analysis set. Following this initial interim futility analysis, subsequent interim futility analyses will be performed after every 10 subjects in Part 2 have reached the data cutoff criteria, until all subjects are enrolled and evaluated. For interim futility analyses a response is defined as either a confirmed or unconfirmed CR or PR per RECIST 1.1. For the final analysis, a response is defined as a confirmed CR or PR per RECIST 1.1.

The Target Value (TV) is set to demonstrate a 18% increase in ORR (ie, TV = 30%) over the benchmark 12% ORR. For Part 2, at final analysis:

- NoGo criteria will be met if the probability that the true ORR exceeds the pre-specified TV of 30% is less than 5% (ie, NoGo: P[ORR > TV] < 5%).

Given the existing observed data during the continuous monitoring stage, the Bayesian predictive probability is obtained by calculating the probability of reaching a NoGo decision should the treatment group be enrolled and evaluated to the maximum planned final sample size of 40 in Part 2. Further enrollment may be terminated if futility criteria are met. Notice the NoGo criteria is for interim futility analysis purpose only.

- Futility is met if it is predicted that there is a high probability of reaching a NoGo decision upon full enrollment of 40 subjects in Part 2 given the existing observed data (ie, predictive probability of a NoGo decision > 95%).

The decision matrix for continuous monitoring of ORR is provided in Figure 9-1 assuming a prior distribution of Beta (1, 1). For example, given TV of 30%, 3 or fewer observed responders after 30 subjects have reached the data cutoff criteria would trigger stopping enrollment claiming futility due to a high probability of reaching a NoGo decision upon full enrollment to 40 subjects given the existing observed data.

Figure 9-1. Decision Matrix for Continuous Monitoring of ORR

Operating characteristics of this continuous monitoring method are presented in Table 9-3 and are based on 100 000 simulations using the prespecified TV value, and NoGo and Futility definitions.

A false NoGo is defined as observing either futility criteria during the continuous monitoring stage or NoGo criteria at final analysis when the true ORR is greater than or equal to the TV (ie, False NoGo: P[Futility or NoGo Decision | True ORR ≥ TV]).

Table 9-3. Guidelines for Futility Analysis

True ORR (BM ORR = 12%)	Probability of Futility	Expected N	% Decision Prior to Final
10%	96%	29	67%
15%	76%	35	35%
20%	44%	38	14%
25%	19%	39	5%
30%	6%	40	1%
35%	1%	40	0%
40%	0%	40	0%

BM ORR = benchmark objective response rate; TV = target value.
Criteria: Target Value (TV) =30%; NoGo: Pr(ORR > TV) < 5%; Futility: PP(NoGo)>95%
Frequency: 10 subjects; BM ORR: Benchmark Objective Response Rate

9.4.1.1.1 Criteria for Evaluating Treatment With Siltuximab

Amgen will conduct evaluations of the treatment and outcome of the CRS events treated with siltuximab on an ongoing basis to assess if the threshold for evaluating siltuximab treatment has been reached as outlined in the Table 9-4. If these criteria are met, an ad hoc DLRM will be triggered to review safety data and available pharmacokinetic, pharmacodynamics, and efficacy data. If recommended by DLRT, the use of siltuximab will resume. The criteria to trigger an adhoc DLRM to review siltuximab treatment use a

Bayesian approach proposed by Thall et al, 1995; an adhoc DLRM will be triggered if the posterior probability that the CRS progression to Grade 3 rate of greater than 20% is > 80% or the posterior probability that the CRS progression to Grade 4 rate of greater than 7.5% is >80%; or observation of any grade 5 CRS after the event has been treated with siltuximab. The boundaries presented below assume a prior distribution of Beta (0.4, 1.6) for progression to grade 3 CRS and a prior distribution of Beta (0.15, 1.85) for progression to grade 4 CRS. The evaluations could occur more frequently if necessary to address emerging safety concerns. If the triggered ad hoc DLRM coincide with regular DLRM, they may be combined.

Table 9-4. The Criteria for Evaluating the Use of Siltuximab

	Trigger DLRM if severity of any CRS event treated with siltuximab progresses to Grade 5	
Number of subjects treated with siltuximab	**Or this number of subjects with severity of CRS progressed to Grade 3 after being treated with siltuximab**	**Or this number of subjects with severity of CRS progressed to Grade 4 after being treated with siltuximab**
5	≥ 3	≥ 2
10	≥ 4	≥ 2
15	≥ 5	≥ 3
20	≥ 6	≥ 3
25	≥ 7	≥ 4
30	≥ 9	≥ 4
35	≥ 10	≥ 5
40	≥ 11	≥ 5

DLRM = Dose Level Review Meeting; CRS = cytokine release syndrome

9.4.1.2 Primary Analysis

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

9.4.1.3 Final Analysis

The final analysis will be performed after the last subject has had an opportunity to complete the corresponding end of treatment (EOT) visit/procedures.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, efficacy 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 and 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 (Brookmeyer and Crowley, 1982) method. Kaplan-Meier methods will be used to estimate landmarks for time to event endpoints (eg, 1-year overall survival [OS]) with the Greenwood formula (Kalbfleisch and Prentice, 1980) used to estimate the standard error used in CI calculation.

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	Listings of secondary efficacy endpoints will be produced for all subjects. The proportion of subjects with an objective response (OR) (per RECIST 1.1 guidelines [Sections 11.8 and 11.9]) and 95% CI will be tabulated by planned dose level. Disease control rate and 95% CI will be tabulated by planned dose level. 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 (DOR), 2) progression-free survival (PFS), 3) OS. For all subjects treated at the MTD and/or RP2D, Kaplan-Meier methods will be used to estimate landmarks for time to event events (eg, PFS and OS at 6 and 12 months) 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 tarlatamab. The analysis of DLTs will be conducted on the DLT Analysis Set. Subject incidence of DLT will be tabulated by planned dose level. The statistical analysis methods for other safety endpoints are in Section 9.4.2.3.

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 **noninvestigational product(s)/auxiliary medicinal product(s)**, and significant treatment-emergent adverse events will also be provided.

9.4.2.3.3 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics at selected time points by treatment group. Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated by treatment group.

9.4.2.3.4 Vital Signs

The analyses of vital signs will include summary statistics at selected time points by treatment group. Shifts in vital sign values between the baseline and the worst on-study value will be tabulated by treatment group.

9.4.2.3.5 Physical Measurements

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

9.4.2.3.6 Electrocardiogram

The ECG measurements from this clinical study are performed as part of standard of care for routine safety monitoring, rather than for the purposes of assessment of potential QTc effect. No statistical analyses of ECG measurements are planned.

[redacted]

9.4.2.3.8 Exposure to Investigational Product

Subject exposure to investigational product and combination therapy will be summarized using descriptive statistics. The number of cycles of protocol-specified therapy administered will be summarized with an additional breakdown of the number of cycles started. In addition, the duration of therapy, the cumulative dose, and the average dose per administration and relative dose intensity will be summarized. The number and percent of subjects with dose modifications (eg, dose reductions, dose interruptions) and reason for modification will be summarized as well. Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given.

9.4.2.4 Other Analyses

For tarlatamab, PK parameters 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, exploratory analyses to describe the relationship between tarlatamab exposure and either PD effect and/or clinical outcome may also be performed. These exploratory analyses may not be part of the clinical study report.

9.4.2.5 Adaptive Design

The guidelines described in Section 4.1 for dose escalation or de-escalation to the next dose level are determined by a mTPI-2 algorithm (Guo et al, 2017)The mTPI-2 algorithm employs a simple beta-binomial Bayesian model. Let p_T be the target toxicity level and ($p_T - \epsilon_1$, $p_T + \epsilon_2$) be the equivalence toxicity interval denoted as EI. The unit toxicity interval (0, 1) is divided into subintervals with equal length given by ($\epsilon_1 + \epsilon_2$). Let the under-dosing intervals (LI) denote for a set of intervals below EI, and the overdosing intervals (HI) for a set of intervals above EI. The 3 types of dosing intervals (EI, LI, HI) are associated with 3 different dose-escalation decisions. The LI correspond to a dose escalation (E), the HI correspond to a dose de-escalation (D), and proper dosing intervals (EI) correspond to staying at the current dose (S). This study design uses a target toxicity level, p_T of 30%, and EI of (25%, 35%).

Decision rules are based on the unit probability mass (UPM) calculated on these equal-length intervals. Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI-2 design calculates the UPMs for the each of equal-length dosing intervals. If the interval with the largest UPM is from LI, EI or HI, then the corresponding dose decision would be E, S, or D, respectively.

A dose level will be considered unsafe, with no additional subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate p_T (ie, P [DLT > p_T | data] > 95%). Based on this rule, the following instances would result in a dose level being considered unsafe.

- 3 or more DLTs in ≤ 4 subjects
- 4 or more DLTs in ≤ 6 subjects
- 5 or more DLTs in ≤ 9 subjects
- 6 or more DLTs in 10 subjects

After the escalation phase is completed, final DLT rates at each dose level will be estimated by isotonic regression (Ji et al, 2010). The weighted least squares regression model will assume monotonic non-decreasing DLT rates with increasing dose and use the empirical (observed) DLT rates at each dose level as responses and dose level sample sizes as weights, along with the pool adjacent violators algorithm (PAVA) to estimate the DLT rate at each dose level. Given the DLT estimates for each dose level, the MTD will be selected from all tried dose levels that have not been previously declared to be unsafe with a decision according to the mTPI decision table. With this constraint, the MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of 30%.

10. References

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody(ies)
ADA-IC	ADA-related immune complexes
ALL	acute lymphoblastic leukemia
[redacted]	
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCG	Bacillus Calmette–Guérin
BIL	bilirubin
BiTE®	bispecific T-cell engager
BM ORR	benchmark objective response rate
BUN	blood urea nitrogen
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CBC	complete blood count
CD	cluster of differentiation
CFR	U.S. Code of Federal Regulations
CI	confidence intervals
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CR	complete response
CRF	case report form
CRO	contact research organization
CRS	cytokine release syndrome
CT	computed tomography
[redacted]	
CTCAE	Common terminology Criteria for Adverse Events
[redacted]	
DILI	drug induced liver injury
DLL3	delta-like protein 3
DLRMs	dose level review meetings
DLRT	Dose Level Review Team

Abbreviation or Term	Definition/Explanation
DLT	dose limiting toxicity(ies)
DOR	duration of response
EU	**European Union**
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
EI	equivalence toxicity interval
EpCAM	epithelial cell adhesion molecule
eSAE	**electronic serious adverse event**
Fc	fragment crystallizable
[redacted]	
FIH	first-in-human
FSH	follicle stimulating hormone
FT4	free thyroxine
[redacted]	
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GSO	Global Safety Officer
HepBsAg	Hepatitis B Surface Antigen
HI	overdosing intervals
HIV	human immunodeficiency virus
HLE	half-life extended
HNSTD	highest non-severely toxic dose
HRT	hormonal replacement therapy
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IFN-γ	interferon gamma
Ig	Immunoglobulin
IGF	insulin-like growth factor
IHC	Immunohistochemistry

Abbreviation or Term	Definition/Explanation
IL-2	Interleukin-2
IL-6	Interleukin-6
INN	International Nonproprietary Name
INR	international normalized ratio
IP	investigational product
IPIM	Investigational Product Instruction Manual
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(ly)
[redacted]	
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LI	under-dosing intervals
LVEF	left ventricular ejection fraction
mCRPC	metastatic castration-resistant prostate cancer
MDRD	modification of diet in renal disease
MMSE	Mini Mental Status Examination
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI-2	modified toxicity probability interval design
MUGA	multigated acquisition
NEPC	neuroendocrine prostate cancer
NLCB	no longer clinically benefiting
OR	objective response
ORR	objective response rate
OS	overall survival
OSF	**Other safety findings**
PAVA	pool adjacent violators algorithm
PCR	polymerase chain reaction
PCWG3	Prostate Cancer Working Group 3
PD	**Progressive disease**
PD-1	programmed cell death protein 1
[redacted]	
PFS	progression-free survival

Abbreviation or Term	Definition/Explanation
PI	principal investigator
PK	pharmacokinetic(s)
PR	partial response
[redacted]	
PTEN	phosphatase and tensin homolog
PTT	partial thromboplastin time
PT	prothrombin time
Q2W	every 2 weeks
QTcF	QT interval by Fredericia
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RR	relapsed/refractory
SAP	statistical analysis plan
scFC	single chain fragment crystallizable
SCLC	small cell lung cancer
SFU	safety follow-up
SoA	Schedule of Assessments
SOI	start of infusion
SS	**Special situations**
$t_{1/2}$	half-life
TBL	total bilirubin
^{99m}Tc-MDP	^{99m}technetium methylene diphosphonate radionuclide
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
TV	target value
ULN	upper limit of normal
UPM	unit probability mass
US	United States

11.2 Appendix 2. Clinical Laboratory Tests

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

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

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

Table 11-1. Analyte Listing

<table>
<tr><th colspan="3">LOCAL/SAFETY LABS</th><th>CENTRAL LABS</th></tr>
<tr>
<td><u>Chemistry</u>
• Sodium
• Potassium
• Chloride
• Bicarbonate or CO2
• Total protein
• Albumin
• Calcium
• Magnesium
• Phosphorus
• Glucose
• BUN (Blood Urea Nitrogen) or Serum Urea
• Creatinine
• Total bilirubin
• Direct bilirubin
• [redacted]
• AST (SGOT)
• ALT (SGPT)
• Creatine kinase
• Uric Acid (only during the first 2 cycles)
[redacted]</td>
<td><u>CBC with differential</u>
• RBC
• Hemoglobin
• MCV
• Platelets
• WBC

<u>Differentials</u>
5-part differential:
• Lymphocytes
• Monocytes
• Eosinophils*
• Basophils*
• Total Neutrophils* or (Segmented neutrophils and bands/stabs)
3-part differential if unable to perform 5-part:
• Lymphocytes
• Granulocytes
• Monocytes
OR
• Lymphocytes
• Neutrophils
• Mid-cell fraction</td>
<td><u>Coagulation</u>
• PT/INR
• Partial Thromboplastin Time (PTT) or Activated Partial Thromboplastin Time (APTT)

<u>Urinalysis</u>
• Blood
• Protein
• Glucose
• Bilirubin

<u>Endocrine safety</u>
• Cortisol (AM sample)
• TSH
• FT4
• FSH
• LH
• Testosterone
Only collected at screening and EOT
• ACTH (AM sample)
• IGF-1
• Prolactin</td>
<td><u>Biomarker analyses</u>
• Cytokines
[redacted]
<u>Other Labs:</u>
• Tarlatamab PK
[redacted]
• Pharmacogenetic (optional)
[redacted]</td>
</tr>
<tr><td colspan="3"><u>Other safety labs</u></td><td></td></tr>
<tr>
<td>• CRP
• Ferritin
• HIV antibody testing
• [redacted]</td>
<td>• Amylase
• Lipase</td>
<td>Hepatitis Serology Testing
• Hep B surface antigen
• Hep C antibody
• Hep B total core antibody</td>
<td></td>
</tr>
</table>

* Local lab may report Granulocytes instead of Neutrophils, Eosinophils, and Basophils individually.
ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; [redacted] EOT = end of treatment; FT4 = free thyroxine; Hep = hepatitis; HIV = human immunodeficiency virus; ICF-1 = insulin-like growth factor receptor 1; INR = international normalized ratio; [redacted] LH = luteinizing hormone; MCV = mean corpuscular volume; [redacted] PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid stimulating hormone; WBC = white blood cell count

11.3 Appendix 3. Study Governance Considerations

Monitoring Committee(s)

Dose Level Review Meetings (DLRM)

A dose level review meeting (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, exploring intermediate doses, cohort continuation, or cohort expansion; making recommendations about non-dose escalation cohorts (eg, expanded, highest dose and/or final cohort); and evaluating safety data for purposes of applying Dose Cohort Stopping Rules. The Dose Level Review Team (DLRT) will make recommendations on implementing step dosing and may modify the premedication regimen based on emerging safety data, including the recommendation to implement additional corticosteroids (dexamethasone 8 mg orally 6 to 16 hours prior to the run-in dose and step dose[s] in cycle 1) based on emerging results from Part D in the ongoing first-in-study (FIH) study (20160323). The DLRT members are the Medical Monitor, Global Safety Officer (GSO), and enrolling Site Investigators. The DLRT will include actively screening and enrolling Site Investigators. The required Medical Monitor, GSO, and Site Investigators are the only voting DLRT members. The following non-voting Amgen representatives also will be part of the DLRT as appropriate: other functional area representatives (eg, clinical study manager, biostatistician, or pharmacokinetic [PK] scientist).

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

For a DLRM to occur, the Medical Monitor must attend, and the GSO or delegate must attend. In addition, a quorum of Site Investigators must attend. A quorum is defined as at least 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 (IP) administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory data, and PK/pharmacodynamic information will be reviewed. In addition to dose limiting toxicities (DLTs), all ≥ grade 3 toxicities not meeting DLT criteria

will be reviewed and may be considered in DLRT recommendations. Data will not need to be source data verified and queries will not need to be resolved prior to the DLRM.

In the expansion phase, all available study data will be reviewed (with recruitment ongoing) by the DLRT after 10 and 20 subjects have at least completed their first treatment cycle plus two weeks or dropped out of treatment /study, whichever occurs earlier. Enrollment in dose expansion may continue while the DLRM preparation and meeting are in progress. Ad hoc meetings may be convened any time in case of important safety events.

Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (eg, subject recruitment advertisements) must be submitted to an **external review body (eg, IRB/IEC/regulatory authorities)** by the investigator and reviewed and approved by the **external review body**. A copy of the written approval of the protocol and ICF 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 **external review body** for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the **external review body** 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 **external review body** annually or more frequently in accordance with the requirements, policies, and procedures established by the **external review body**
- Obtaining annual **external review body** approval/renewal throughout the duration of the study. Copies of the investigator's reports and the **external review body** continuance of approval must be sent to Amgen

- Notifying the **external review body** 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 **external review body**, and all other applicable local regulations

Informed Consent Process

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

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

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

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 ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

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

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

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF 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 ICF if the rescreening occurs within 28 days from the previous ICF signature date.

The 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 ICFs) 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 **external review body** 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.

Serious Breach

Suspected Serious Breaches must be reported to the study team or the Clinical Out-of-Hours Support Program: https://wwwext.amgen.com/science/clinical-trials/clinical-out-of-hours-support-program immediately and no later than 1 calendar day from the time of awareness.

A Serious Breach is a breach of any of the following:

- **Good Clinical Practice**
- **the clinical trial protocol**
- **an applicable regulation**

That is likely to impact to a significant degree either of the following:

- **the safety, physical, or mental integrity and the rights of the subject**
- **the reliability and robustness of the data and the scientific value of the trial**

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.

Results Reporting

Results will be reported to clinical study registries in accordance with applicable regulatory requirements. The final summary results will be reported after the global end of study (as defined in Section 4.4) to ensure data from all sites globally are included in the reported results.

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, **external review body** 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, **investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s)** 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 must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

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

Source Documents

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

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

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

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

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

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

Elements to include:

- Subject files containing completed CRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the **external review body** 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 **external review body** 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 statistical analysis plan (SAP).

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram (ECG), 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 **intentional** overdose of either study treatment or a concomitant medication. • **Intentional** overdose will be reported as an adverse event/serious adverse event **when** it is taken with possible suicidal/self-harming intent. Such **intentional** overdoses are to be reported regardless of sequelae **on the Events CRF**. • **Accidental/unintentional overdose will be captured as a Medical Error.** • For situations when an adverse event or serious adverse event is due to neuroendocrine prostate 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.

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.

Other Safety Findings/Special Situations: Medication Errors, Misuse or Abuse	
All medication errors, misuse or abuse of the investigational product when associated with a serious adverse event, the Other Safety Findings (OSF)/Special Situations (SS) must be reported to Amgen or designee immediately and no later than 24 hours of the investigator's awareness by submitting paper-based Clinical Trail electronic Serious Adverse Event (eSAE) Contingency Report Form.	
Definitions	**Medication Error: A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the participant (eg, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice).**
	Misuse: A misuse refers to situations where the medicinal product, combination product, or medical device is intentionally and inappropriately used not in accordance or outside what is foreseen in the protocol.

	Abuse: An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, combination product, or medical device, which is accompanied by harmful physical or psychological effects.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF).
- The investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Did the event start prior to the first dose of investigational product;
  - Assessment of Seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product **and/or, noninvestigational product(s)/auxiliary medicinal product(s)**;
  - **Assessment of relatedness to study-required activity and/or procedures is only required for Serious Adverse Events;**
  - Action taken; and.
  - Outcome of event
- If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event electronic case report form (eCRF).
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contact research organization (CRO) 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 4.0 which is available at the following location:

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

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product **and noninvestigational product(s)/auxiliary medicinal product(s),** and each occurrence of each adverse event.
- **The investigator is obligated to assess the relationship between investigational product(s), and noninvestigational product(s)/auxiliary medicinal product(s), study-required activity and/or procedure(s) and each occurrence of each 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 (IB) 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 **they have** reviewed the adverse event/serious adverse event and has provided an assessment of causality. **For sites reporting serious adverse events via electronic data capture (EDC), the investigator or sub-investigator must confirm causality in EDC within 72 hours of the serious adverse event being entered on the Events CRF.**
- 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 **their** opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. **In this case, for sites reporting serious adverse events via EDC, the investigator or sub-investigator must reconfirm causality in the EDC system within 72 hours of the serious adverse event being entered on the Events CRF.**
- 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 **investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s)** 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 **immediately and no later than** 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 EDC system.
- If the EDC system is unavailable, then the site will report the information to Amgen using a **paper-based** Serious Adverse **Event** Contingency Report Form **(also referred to as the** electronic Serious Adverse **Event** Contingency Report Form) (see Figure 11-1) **immediately and no later than** 24 hours of the investigator's **awareness** of the event.
- **The primary mechanism for the site to report the Other Safety Finding/Special Situation associated with a serious adverse event to Amgen is by submitting the Clinical Trial eSAE Contingency Report Form immediately and no later than 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 Serious Adverse Event Report Form.
- Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen **immediately and no later than 24 hours of** the investigator**'s awareness** of **the** 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 Form

AMGEN Study # 20200040 AMG 757 Tarlatamab	Clinical Trial Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Notify Amgen Immediately and no later than 24 Hours of awareness of the serious adverse event/ other safety finding/special situation

Reason for reporting this event using the Serious Adverse Event Contingency Report Form:

The Clinical Trial Database (e.g. Rave):

- ☐ Is not available due to internet outage at my study site
- ☐ Is not yet available for this study
- ☐ Has been closed for this study
- ☐ Other Safety Finding/Special Situation associated with a Serious Adverse Event

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

<<Amgen Safety Fax Number to be populated by the Study Manager/Protocol Author/designee prior to providing to sites: SELECT OR TYPE IN A FAX#>>

If an email address or eFax is used, the Primary Study Team (e.g., Clinical Manager or Delegate) will need to ensure secure email exchange is established between the Provider/Study Sites Vendor/Supplier, Sites and Amgen.

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		

3. SERIOUS ADVERSE EVENT or Other Safety Finding/Special Situation associated with a 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 OR Other Safety Finding/Special Situation associated with a Serious Adverse Event *List one event per line.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or the investigational medical device? Tabzmab No/Yes/	GoPSMA No/Yes/	<Pickvar> No/Yes/	<Pickvar> No/Yes/	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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AMGEN
Study # 20200040
AMG 757 Tarlatamab

Clinical Trial Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Site Number	Subject ID Number

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

IP/ 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 #
Tarlatamab	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Ge-PSMA	☐ blinded ☐ open label							Lot # ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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

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AMGEN Study # 20200040 AMG 757 Tarlatamab	Clinical Trial Electronic Serious Adverse Event Contingency Report Form For Restricted Use

	Site Number	Subject ID Number	

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

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

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11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy Information

Study-specific contraception requirements for males are outlined in Section 5.2.

Male subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they father a child during treatment and for **60** days after the last dose of **investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s)**.

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with **investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s)**; 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 **60** days after the last dose of **investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s)**

The female partner should consider using an acceptable method of effective contraception such as: hormonal, intrauterine device (IUD), intrauterine hormonal-releasing system (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.

Definition of Females of Childbearing Potential (for female partners of male subjects)

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.

Unacceptable Methods of Birth Control for Male 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

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 **60** days after discontinuing **investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s)**, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety **immediately and no later than** 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.

Figure 11-2. Pregnancy Notification Form

Amgen Proprietary - Confidential

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: 20200040

Study Design: [X] 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 757				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

11.6 Appendix 6. Sample Storage and Destruction

Any blood, tumor, biomarker, or pharmacokinetics (PK) samples collected according to the Schedule of Activities (Section 1.3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand tarlatamab, the dose response and/or prediction of response to tarlatamab, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining 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. Reporting and Management of potential Hepatotoxicity

Subjects with abnormal hepatic laboratory values **such as** alkaline phosphatase **(**ALP**)**, aspartate aminotransferase **(**AST**)**, alanine aminotransferase **(**ALT**)**, total bilirubin **(**TBL) and/or international normalized ratio (INR) and/or signs **and** symptoms of **hepatotoxicity** (as described below) may meet the criteria for **interruption** or permanent discontinuation of Amgen investigational product or **noninvestigational product(s)/auxiliary medicinal product(s)**. **This instruction is based on** the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Reporting and management of hepatotoxicity in subject participating in clinical trials is described below and management is summarized in the flow chart in subsection 11.7.6.

11.7.1 Criteria for stopping Amgen Investigational Product and noninvestigational product(s)/auxiliary medicinal product(s) Due to Potential Hepatotoxicity

Stopping rules apply to **each of the following criteria in** subjects for whom another cause **for the** changes in liver biomarkers (total bilirubin [TBL], international normalized ration [INR], and transaminases) has not been identified.

- ALT **or** AST > 8xULN
- ALT or AST **>** 5xULN **for more than** 2 weeks
- ALT **or** AST **> 3xULN and (TBL >2xULN or INR >1.5)**
- **ALT or AST > 3xULN with the appearance of fatigue,** nausea, vomiting, right upper quadrant pain **or tenderness,** fever**, rash, and/or eosinophilia (>5%).**

Of note in subjects with elevated values at baseline (before exposure to the investigational medicinal product), fold increases above the baseline values will guide the interruption and close observation.

11.7.2 Reporting **Criteria**

Cases with events of elevation of AST**,** ALT**,** TBL**,** INR, **mentioned** above, require the following:

- The event is to be reported to Amgen as a serious adverse event **immediately and no later than** 24 hours **after** discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate Case Report Form (CRF) (eg, Event**s electronic Case Report Form [e**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 **potential** hepatotoxicity are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 11.4.

11.7.3 Follow up Actions

All subjects in whom investigational product(s) or **noninvestigational product(s)/auxiliary medicinal product(s)** is/are **interrupted** (either permanently or conditionally) due to potential **hepatotoxicity should be** undergo a period of "close observation" until **elevated laboratory values** return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, BIL (total and direct), and INR within 24 hours.
- In cases **in which laboratory values are still elevated** perform **repeat measurement of liver lab tests** every **2 to 3 days** until laboratory abnormalities improve.

Testing frequency of the above laboratory tests may decrease if the **laboratory** abnormalities stabilize**,** or the investigational product(s) or **noninvestigational product(s)/auxiliary medicinal product(s)** has/have been discontinued AND the subject is asymptomatic.

The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of study drug (s).

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

Initiate investigation of alternative causes **for hepatotoxicity (Section 11.7.3.1).**

If laboratory values improve, consider rechallenging with the study drug(s) only if the benefit: risk ratio is supportive (and as described in Section 11.7.4). Otherwise, discontinue study drug(s) permanently.

11.7.3.1 Investigating Alternative Causes of Hepatotoxicity

The following **assessment** are to be considered depending on the clinical situation:

- **B**lood 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:

- **p**rior and/or concurrent diseases or illness
- **e**xposure to environmental and/or industrial chemical agents
- **s**ymptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting**,** and fever**.**
- **p**rior and/or concurrent use of alcohol, recreational drugs**,** and special diets**.**
- **c**oncomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms

- Viral serologies**.**
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear**.**
- Appropriate liver imaging if clinically indicated**.**
- Appropriate blood sampling for pharmacokinetic (PK) analysis if this has not already been collected**.**
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)**.**

11.7.3.1.1 Important Alternative Causes

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

- **h**epatobiliary tract disease
- **v**iral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, **c**ytomegalovirus, **h**erpes **s**implex **v**irus, **v**aricella, **t**oxoplasmosis, and **p**arvovirus)
- **r**ight-sided heart failure, hypotension or any cause of hypoxia **to** the liver causing ischemia.
- **e**xposure to hepatotoxic agents/drugs **or hepatotoxins**, including herbal **and** dietary supplements, plants and mushrooms.
- **h**eritable disorders causing impaired glucuronidation (eg, Gilbert's **s**yndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- **a**lpha-one antitrypsin deficiency
- **a**lcoholic hepatitis
- **a**utoimmune hepatitis
- Wilson's disease and hemochromatosis
- **NASH (n**onalcoholic fatty liver disease **AKA MASH) including steatohepatitis**
- **n**on-hepatic causes (eg, rhabdomyolysis, hemolysis)

Special consideration is warranted when using products known to cause transient elevation of liver enzymes, such as T cell engager molecules (TCE). For example, in the instances of cytokine release syndrome (CRS) following exposure to BiTE molecules, transient elevations of isolated liver parameters were frequently noted.

Careful monitoring of laboratory parameters and the clinical status of patients is required, and continuation of the medication maybe considered and will be at the discretion of the investigators.

11.7.4 Rechallenge and Dose Modification in Patients with suspected hepatotoxicity in Oncology Trials

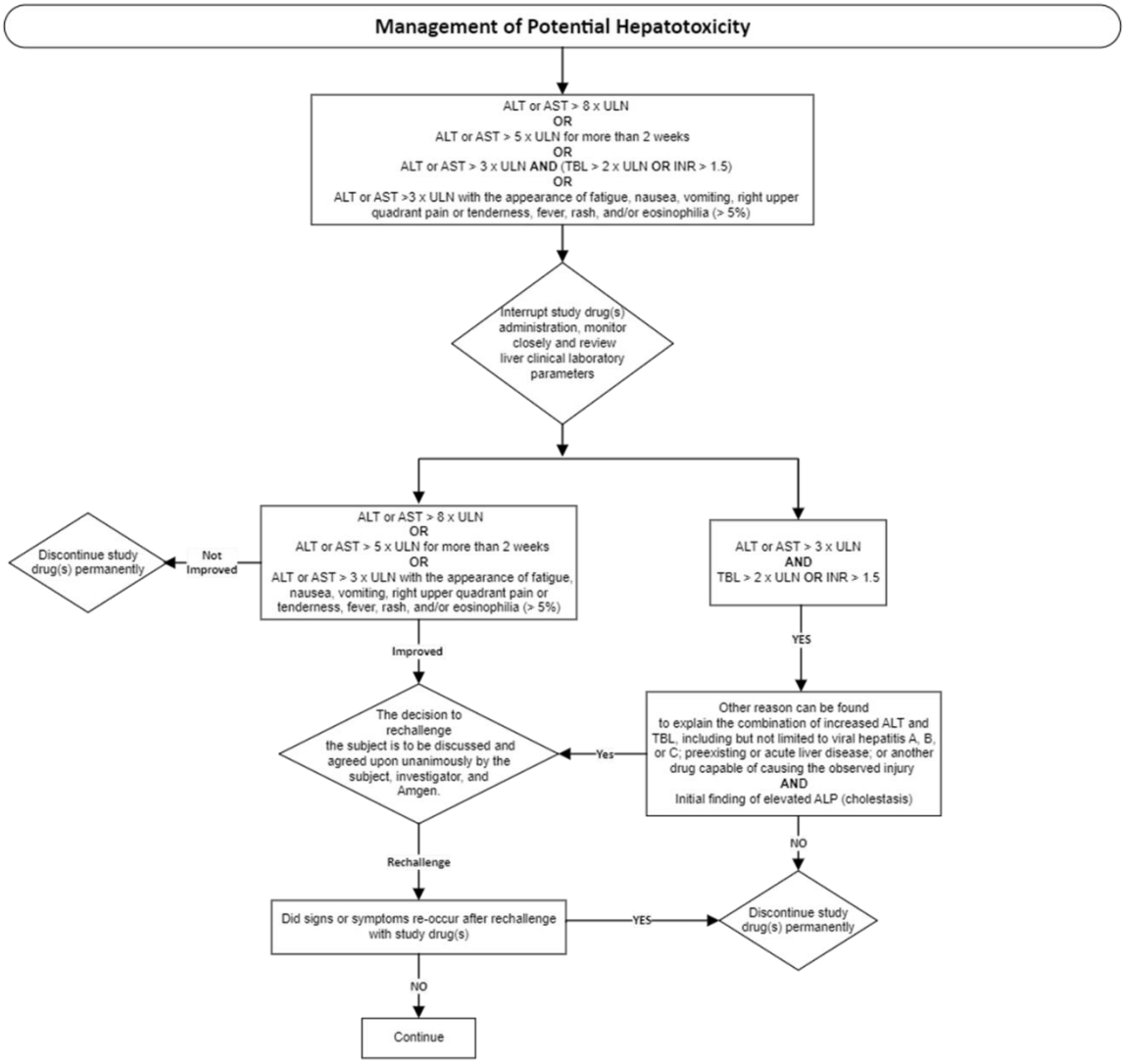
- The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen**. If rechallenge is considered appropriate, the subject must be fully informed about the risk and should give written consent. Any rechallenge must be accompanied by close monitoring, with at least weekly liver biochemistry until response to the rechallenge is fully characterized.**
- If signs or symptoms recur with rechallenge, then Amgen investigational product and noninvestigational product(s)/auxiliary medicinal product(s), as appropriate is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation are never to be rechallenged**.**
- **For oncology drugs that demonstrate potential benefit but also potential hepatotoxicity, consideration of rechallenge or dose modification (with a reduced dose) should be based on benefit: risk and clinical and biochemical characteristics of the original liver injury.**
- **Rechallenge is not recommended when there is no evidence of benefit for the individual subject, or where alternative treatment options are available.**
- **Rechallenge is generally not recommended for cases of suspected or confirmed severe hepatocellular injury (clinical evidence of liver dysfunction with jaundice or INR elevation), in the presence of underlying cirrhosis, or where there are features of immunologic hepatotoxicity.**
- **Before undertaking a rechallenge, there should be sufficient resolution of liver biochemistry abnormalities; although these depend on the patient population, reasonable options include ALT reducing to < 3x ULN for those with normal baseline ALT or returning to < 4x ULN and < 6x ULN for those with elevated baseline ALT of 1.5 to 3x ULN and 3 to 5x ULN, respectively.**

11.7.5 Permanent Discontinuation of Study Drug(s)

In the absence of acceptable enzyme level decrease or lack of a plausible alternative explanation for the elevated lab pattern, consider permanent discontinuation of study drug treatment.

11.7.6 Management Flow Chart

The following flow chart can be used to manage potential hepatotoxicity cases.


Management of Potential Hepatotoxicity
ALT or AST > 8 x ULN
OR
ALT or AST > 5 x ULN for more than 2 weeks
OR
ALT or AST > 3 x ULN AND (TBL > 2 x ULN OR INR > 1.5)
OR
ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
Interrupt study drug(s) administration, monitor closely and review liver clinical laboratory parameters
ALT or AST > 8 x ULN
OR
ALT or AST > 5 x ULN for more than 2 weeks
OR
ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
Not Improved
Discontinue study drug(s) permanently
ALT or AST > 3 x ULN
AND
TBL > 2 x ULN OR INR > 1.5
YES
Improved
Other reason can be found to explain the combination of increased ALT and TBL, including but not limited to viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury
AND
Initial finding of elevated ALP (cholestasis)
Yes
The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.
NO
Rechallenge
Did signs or symptoms re-occur after rechallenge with study drug(s)
YES
Discontinue study drug(s) permanently
NO
Continue

11.8 Appendix 8. Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

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

Methods of Measurement

- Measurement of Lesions - The longest diameter of selected lesions should be measured in the plane in which the images were acquired (axial plane). All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 4 weeks before study day 1.
- Methods of Assessment - The same method of assessment and the same technique should be used to characterize each identified and reported lesion throughout the trial.
- CT/MRI – Contrast-enhanced CT or MRI should be used to assess all lesions. Optimal visualization and measurement of metastasis in solid tumors requires consistent administration (dose and rate) of intravenous (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.
  - A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference by which to characterize objective tumor response.
- Non-target Lesions - All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, and these lesions should be followed as “present”, “absent”, or “unequivocal progression” throughout the study. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (CRF) (eg, “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Response Criteria

Evaluation of Target Lesions

* Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
* Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
* Progressive Disease (PD):	At least a relative 20% increase and an absolute increase of 5 mm in the sum of the diameters of target lesions, taking as reference the smallest sum on study, or the appearance of 1 or more new lesions.
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters since the treatment started.

Evaluation of Non-target Lesions

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

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

Evaluation of Overall Response

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

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

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

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

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

Time Point Response: Subjects With Non-Target Disease Only

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

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

CR = complete response; NE = Not evaluable; PD = progressive disease; SD = stable disease.

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

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

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

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

Special Notes on Response Assessment

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

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

- In some circumstances it may be difficult to distinguish residual disease from scar or normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be further investigated by fluorodeoxyglucose-positron emission tomography (FDG-PET) or PET/computed tomography (PET/CT), or possibly fine needle aspirate/biopsy, to confirm the CR status.

Confirmation Measurement / Duration of Response

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

11.9 Appendix 9. RECIST 1.1 With Prostate Cancer Working Group 3 (PCWG3) Modifications

Imaging provides critical information on disease distribution, prognosis, extent, biology, and host reaction to the tumor. Detailed imaging instructions are provided in the imaging manual. The following Prostate Cancer Working Group 3 (PCWG3) recommendations are provided as a reference (Scher et al, 2016):

Baseline by Site of Disease

PCWG3 retains the PCWG2 recommendations with modifications that include developing, recording, and validating measures of disease burden. Imaging of the chest, abdomen, and pelvis using a contrast-enhanced computed tomography (CT) scan with ≤ 5-mm axial slices is advised for all subjects. For those intolerant of contrast, a cross-sectional magnetic resonance imaging (MRI) scan of the abdomen and pelvis, with a noncontrast CT scan of the chest, may be considered. In phase I and II trials, recognizing that individual lesions may be biologically distinct, PCWG3 recommends reporting whether progression on entry was in the growth of pre-existing lesions, the development of new lesions, or both. PCWG3 advises following Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for extraskeletal disease but recommends that up to 5 lesions per site of metastatic spread (eg, lung, liver, lymph nodes as separate sites) be recorded to address disease heterogeneity and to track patterns of metastatic progression. Bone lesions should be recorded separately.

Prostate or prostate bed

Specific imaging of the prostate or prostate bed is not required for every subject. If there is a question of locally persistent or recurrent disease, a directed MRI of the prostate or prostate bed and/or biopsy of the site is recommended.

Nodes or viscera

PCWG3 advises that nodal disease be measured in the short axis and recorded by location: pelvic disease should be classified as locoregional, and extrapelvic disease (retroperitoneal, mediastinal, thoracic, or other) as metastatic. Nodes ≥ 1.5 cm in the short axis are considered pathologic and measurable. As per RECIST 1.1, lymph nodes that are ≥ 1.0 cm but less than 1.5 cm in the short axis may be pathologic and can be considered nonmeasurable/nontarget lesions. Visceral disease in metastatic subjects should be designated separately as lung, liver, adrenal, or central nervous system (CNS) and is considered measurable if an individual lesion is ≥ 1 cm in its longest dimension.

Given that lung metastases are relatively frequent in metastatic castration-resistant prostate cancer (mCRPC) trials (7% prevalence), chest CT imaging is recommended.

Bone

The use of ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) radionuclide bone scintigraphy as the standard for bone imaging is retained in PCWG3, with the presence or absence of metastasis recorded first. A quantitative measure of disease burden, such as lesional number, the bone scan index, or lesion area is also suggested, recognizing that these measures require further analytical and prospective clinical validation. Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial.

Neurologic

PCWG3 upholds the PCWG2 recommendation to perform an MRI or CT of the brain for subjects with small-cell/neuroendocrine tumors and to maintain a low threshold for performing an MRI of the base of the skull or spine to diagnose and/or detect impending neurologic compromise. Routine imaging of the brain for adenocarcinoma is not recommended.

Type of progression at entry into a trial

PCWG3 advises recording whether progression was manifested by prostate-specific antigen (PSA) alone, bone ± nodes by location, nodes by location only, or viscera (± other sites), and the proportion of subjects who progress in each of these categories, because this is prognostic. PCWG3 also advises reporting whether progression by imaging at study entry involved the growth or enlargement of pre-existing lesions, the development of new lesions, or both.

NLCB: Progression Versus The Decision To Discontinue Therapy

PCWG2 encouraged the continuation of treatment if a rising PSA or worsening of an isolated disease site that was not clinically significant was the sole indicator of disease progression and the subject was otherwise tolerating therapy. Now, recognizing the biologic heterogeneity of individual metastatic lesions, PCWG3 draws the distinction between documenting progression for consistency of reporting (eg, recording the date of

documented progression in a site of disease such as a lymph node that is unlikely to adversely affect prognosis) versus the decision to stop therapy.

To address this, PCWG3 introduces the no longer clinically benefiting (NLCB) reporting metric defined as the date and the specific reason(s) a therapy was ultimately discontinued. This end point permits individualized provider-patient decisions to continue or discontinue a treatment based on the primary therapeutic objective for which it is being administered and assessed, be it quality of life, PROs, or survival. As an example, in cases in which multiple sites of disease continue to respond but 1 to 2 sites grow, focal therapy such as radiation or surgery could be administered to the resistant site(s) and systemic therapy continued. Similarly, therapy may be continued if progression by PSA or imaging is slow and the disease-related symptoms that were present at baseline remain controlled. Important here is to record in detail the specific reasons why a therapy was ultimately discontinued, which may include clinical deterioration (clarifying whether it is disease or therapy related) or need for a change in systemic therapy. PCWG3 cannot define the risks/benefits at the individual level for continuation of therapy beyond progression, but sets the goal of prospectively defining the circumstances in which scenarios are identified where continuing a therapy is justified. Clinical trials evaluating whether therapy a should be stopped and a new one started, continued alone, or continued with a new one added, are ongoing.

Source: Scher et al, 2016.

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. New York Heart Association Functional Classification

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

11.12 Appendix 12. Adaptive Design

The guidelines described in Section 4.1 for dose escalation or de-escalation to the next dose level are determined by a mTPI-2 algorithm (Guo et al, 2017). The mTPI-2 algorithm employs a simple beta-binomial Bayesian model. Let p_T be the target toxicity level and (p_T − ϵ1, p_T + ϵ2) be the equivalence toxicity interval denoted as EI. The unit toxicity interval (0, 1) is divided into subintervals with equal length given by (ϵ1 + ϵ2). Let the under-dosing intervals (LI) denote for a set of intervals below EI, and the overdosing intervals (HI) for a set of intervals above EI. The 3 types of dosing intervals (EI, LI, HI) are associated with 3 different dose-escalation decisions. The LI correspond to a dose escalation (E), the HI correspond to a dose de-escalation (D), and proper dosing intervals (EI) correspond to staying at the current dose (S). This study design uses a target toxicity level, p_T of 30%, and EI of (25%, 35%).

Decision rules are based on the unit probability mass (UPM) calculated on these equal-length intervals. Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI-2 design calculates the UPMs for the each of equal-length dosing intervals. If the interval with the largest UPM is from LI, EI or HI, then the corresponding dose decision would be E, S, or D, respectively.

A dose level will be considered unsafe, with no additional subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate p_T (ie, P [DLT $> p_T$ | data] $> 95\%$). Based on this rule, the following instances would result in a dose level being considered unsafe.

- 3 or more DLTs in ≤ 4 subjects
- 4 or more DLTs in ≤ 6 subjects
- 5 or more DLTs in ≤ 9 subjects
- 6 or more DLTs in 10 subjects

After the escalation phase is completed, final DLT rates at each dose level will be estimated by isotonic regression (Ji et al, 2010). The weighted least squares regression model will assume monotonic non-decreasing DLT rates with increasing dose and use the empirical (observed) DLT rates at each dose level as responses and dose level sample sizes as weights, along with the pool adjacent violators algorithm (PAVA) to estimate the DLT rate at each dose level. Given the DLT estimates for each dose level, the MTD will be selected from all tried dose levels that have not been previously declared to be unsafe with a decision according to the mTPI decision table. With this

constraint, the MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of 30%.

Amendment 7

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager AMG 757 in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer

Amgen Protocol Number Tarlatamab (AMG 757) 20200040

EU CT Number 2024-513316-10

NCT Number NCT04702737

Amendment Date: 21 June 2024

Rationale:

This protocol has primarily been amended to include the following changes:

- Update details about Protocol Approver and Key Sponsor Contact
- Remove EudraCT Number from the title page of the protocol.
- Align the protocol with the latest clinical protocol template.
- Remove 2 and 3 step dosing of cycle 1 scheduling tables (i.e. Table 1-1), Schedule of Activities tables (i.e. Table 1-3, Table 1-4), overall design Section 4.1 and step dosing Section 6.2.1.2.1.
- Update footnote e and ff for SoA table.
- Update Safety Follow-Up visit from 42 (±5) days to 60 (+5) days.
- Remove Section 2.3.1.4 and Section 6.8.1 sucrose medicated renal impairment.
- Update provision of investigational product in Section 4.4.1
- Update male subjects use of contraception, use of condom and donating sperm timing from 132 days after the last dose of tarlatamab to 60 day after the last dose of tarlatamab.
- Update the title and content of Noninvestigational Products/Auxiliary Medicinal Products Section to be in accordance with European Union Clinical Trials

Regulation (EU CTR) and modify the wording “protocol-required therapy” to “noninvestigational product(s)/auxiliary medicinal product(s)”

- Remove Section 6.1.3, Other Protocol Required Therapies as this section is not applicable in this study.
- Remove live and live-attenuated vaccines during study drug therapy from exclusion criteria.
- Update serious and fatal serious adverse events collection, recording, and reporting period to sponsor to be immediately and no later than 24 hours rather than within 24 hours.
- Add Section 8.2.3.4.2, Hypersensitivity as other safety measure.
- Add Serious Breach in Appendix 3, SAE related information, Results Reporting in the protocol to align with the latest clinical protocol template.
- Other Safety Findings/Special Situations language has been added to Section 8.2.4.6 and Section 11.4 (Appendix 4).
- Update electronic Serious Adverse Event Contingency Form in Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-Up and Reporting, Figure 11-1. Sample Electronic Serious Adverse Event Contingency Form.
- Update Section 11.7, Appendix 7. Reporting and Management of potential Hepatotoxicity.
- Update Section 11.8, Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Evaluation of Non-target Lesions table.

Amendment 6

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager Tarlatamab in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer (DeLLpro-300)

Amgen Protocol Number (AMG 757) 20200040

EudraCT Number 2020-003508-15

NCT Number: NCT04702737

Amendment Date: 29 September 2022

Rationale:

The protocol is being amended to address further biomarker exploration with the addition of a prospectively selected delta-like protein 3 (DLL3) + neuroendocrine prostate cancer (NEPC) cohort (n ~ 40 subjects). Applicable sections of the protocol are being modified to address this addition to the study and the subsequent analyses associated with the new cohort. Changes including, but not limited to, the following are being incorporated into the protocol:

- Added language to incorporate prospective DLL3 selection in the eligibility criteria, biomarker assessment and all other related sections
- Added language to align aspects of data collection and monitoring across the tarlatamab program
- Key safety information updated to include immune effector cell associated neurotoxicity syndrome and reference to the investigator brochure for complete information
- Removal of schedule of activities (SOA) tables for 2-step and 3-step-dosing and the inclusion of a SOA table for extended intravenous (eIV) dosing
- Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document

Amendment 5

Protocol Title: **A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager AMG 757 in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer**

Amgen Protocol Number AMG 757 20200040

EudraCT number: 2020-003508-15

NCT Number: NCT04702737

Amendment Date: 20 December 2021

Rationale:

This protocol is being amended to address site shortages of tocilizumab. Applicable sections of the protocol are being modified to clarify the use of siltuximab in place of tocilizumab for the treatment of potential cytokine release syndrome (CRS) during a treatment-related adverse event. Tarlatamab clinical experience and safety guidance is being updated. Language is being included throughout to update/clarify the protocol. Changes including, but not limited to, the following are being incorporated into the protocol:

- Added language to include neutropenia as a risk following study treatment administration and guidance for treatment of neutropenia.
- Criteria for use of siltuximab in place of tocilizumab, justification for the proposed dose and schedule, safety stopping rules, and guidance throughout the protocol are being included.
- Table 6-4, “Tarlatamab Dose Modification Guidelines for Adverse Events” is being added.
- Updated language on recording and reporting of serious adverse events.
- Administrative, typographical, and editorial changes have been made throughout the protocol.

Amendment 4

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager AMG 757 in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer

Amgen Protocol Number (AMG 757) 20200040

Amendment Date: 19 April 2021

Rationale:

The protocol is being updated:

- Due to updates in the mean half-life estimate for AMG 757 [redacted] the time to the safety follow up visit from the last dose of AMG 757 and the guidance on contraception for males and female partners have been updated.
- Updated the Secondary Endpoints to include Disease Control Rate
- To align with the ongoing first in human (FIH) study (study 20160323), additional exclusion criteria have been added, including "Has evidence of interstitial lung disease or active, non-infectious pneumonitis" and “Live vaccine therapy within 4 weeks prior to study drug administration".
- To allow for subjects with recurrent Grade 3 abnormalities that are not considered clinically significant or that can be managed with supportive care, the protocol has been updated to allow subjects with recurrent Grade 3 laboratory parameters not considered clinically relevant or recurrent non-febrile Grade 3 neutropenia which resolves with supportive care to grade $\leq$ 1 or to baseline values within 3 weeks to remain on study. Additionally the protocol has been updated to allow for the use of growth factors, such as erythropoiesis-stimulating proteins as well as granulocyte colony stimulating factor (G-CSF), throughout the study as needed.
- Removed 1 Exclusion criterion meant for female subjects of childbearing potential, since this study will allow only male subjects.

[redacted]

- Updated section 2.2.2.3 (Background Clinical Experience with Amgen Investigational Product AMG 757), based on emerging clinical data from the ongoing FIH study (20160323).
- To allow for the subject’s legally authorized representative to sign the consent on their behalf.
- The number of investigative sites was increased from approximately 20 to approximately 25.

[redacted]

- Clarified that ECG measurements from this clinical study are performed as part of standard of care for routine safety monitoring, rather than for statistical analysis.
- Updated the Dose Cohort Levels that may be explored in Table 4-1 based on results from study 20160323 in small cell lung cancer
- Updated the toxicity interval in the mTPI-2 design. Updated Escalation/De-escalation guidelines (Table 4-2) and the decision rule when a dose level will be considered unsafe based on the mTPI2 design.
- Added a table of operating characteristics for the mTPI2 design (Table 4-3), so that it is clear how this design performs under given hypothetical true DLT rates.
- Added Management and restrictions for Covid-19 and vaccines
- To make editorial and formatting changes as applicable.

Amendment 3

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager AMG 757 in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer

Amgen Protocol Number (AMG 757) 20200040

Amendment Date: 10 December 2020

Rationale:

The protocol is being updated:

- To add IV hydration at week 3 day 15 in Tables 1-2 and 1-3.
- To update Table 1-6 to include new footnotes and a central and biomarker laboratory test.
- To correct the abbreviations in the exploratory endpoints.
- To add safety language related to Coronavirus Disease 2019 (COVID-19) in the risk-benefit section.
- To clarify on the laboratory assessment collection timepoint.
- To remove the list of procedures performed at safety follow-up period section.
- To clarify that Mini-Mental Status Examination (MMSE) Version 2 will be performed as a part of the clinical evaluation.
- To remove the language stating that radiological imaging assessment will be performed every 12 weeks for response assessment only in the dose exploration phase.
- To clarify the sponsor responsibility for reporting of serious adverse events.
- To remove the language about requirement of local laboratory results only in the absence of central laboratory results in Appendix 11.2.
- To further clarify on the Dose Level Review Team (DLRT) recommendations on premedication based on emerging results from an ongoing first-in-human (FIH) study (20160323) in Appendix 11.3.
- To make editorial and formatting changes as applicable.

Amendment 2

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager AMG 757 in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer

Amgen Protocol Number (AMG 757) 20200040

Amendment Date: 09 October 2020

Rationale:

This protocol is being updated:

- To add prophylaxis with intravenous (IV) hydration immediately after doses in cycle 1
- To restrict the [redacted] collection timepoints at day 1 of cycles 1 and 4, and at end of treatment (EOT).
- To make editorial and formatting changes as applicable.

Amendment 1

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Delta-like Protein 3 Half-life Extended Bispecific T-cell Engager AMG 757 in Subjects with De Novo or Treatment Emergent Neuroendocrine Prostate Cancer

Amgen Protocol Number (AMG 757) 20200040

Amendment Date: 15 September 2020

Rationale:

This protocol is being updated based on Food and Drug Administration (FDA) requested changes.

Approval Signatures

Document Name: Protocol Amendment tarlatamab 20200040 7

Document Description: AMG 757 Study 20200040 Global Protocol Amendment 7

Document Number: CLIN-000086419

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Document Approvals	
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