Title Page

Protocol Title:		A Phase 1b Study Evaluating the Safety and Efficacy of AMG 757 in Combination with AMG 404 in Subjects with Small Cell Lung Cancer (SCLC)
Short Protocol Title:		AMG 757 and AMG 404 in Subjects with Small Cell Lung Cancer (SCLC)
Protocol Number:		20200439
Investigational Product:		Tarlatamab (AMG 757), AMG 404
Trade Name:		Not Applicable
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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 and Efficacy of AMG 757 in Combination with AMG 404 in Subjects with Small Cell Lung Cancer (SCLC), dated **05 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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Title and Role of Investigator

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1b Study Evaluating the Safety and Efficacy of AMG 757 in Combination with AMG 404 in Subjects with Small Cell Lung Cancer (SCLC)
Short Protocol Title: AMG 757 and AMG 404 in Subjects with Small Cell Lung Cancer (SCLC)

Study Phase: 1b

Indication: Small cell lung cancer (SCLC)

Rationale

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 (Owen et al, 2019). Tarlatamab (International Nonproprietary Name [INN]; AMG 757) is a half-life extended (HLE) bi-specific T-cell engager (BiTE®) molecule 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) Fc (fragment crystallizable; single chain fragment crystallizable [scFc]) region. Currently, tarlatamab is being evaluated in a phase 1 study (Study 20160323) of subjects with small cell lung cancer (SCLC).

AMG 404 is a fully human antibody that binds human programmed cell death-1 (PD-1) with high affinity and blocks the ability of this receptor to interact with its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). AMG 404 has been evaluated as a monotherapy agent in a phase 1 study (Study 20180143) of subjects with advanced or metastatic solid tumors.

Pembrolizumab (Keytruda®) and nivolumab (Opdivo®), both antibodies blocking human PD-1, were approved by the **United States food and drug administration (**US FDA**)** under the accelerated approval program for treatment of patients with metastatic SCLC who have progression after platinum-based chemotherapy and at least 1 other line of therapy (Keytruda® **United states prescribing information [**USPI**]**, 2020; Opdivo® USPI, 2019), based on relatively low response rates (19% with pembrolizumab and 12% with nivolumab; Keytruda® USPI, 2020; Opdivo® USPI, 2019). However, both approvals were subsequently withdrawn after confirmatory studies did not meet their primary endpoint of overall survival (OS) (Merck, 2021; Bristol Myers Squibb, 2020). These data

suggest that immune checkpoint inhibition may need to be combined with other therapies in second line or later.

The combination of tarlatamab and anti-PD-1 antibodies increases T-cell mediated redirected lysis of tumor cells that express DLL3 in vitro as compared to tarlatamab alone. In addition, upregulation of PD-1/PD-L1 in the tumor microenvironment is a mechanism of resistance to BiTE® therapy that treatment with anti-PD-1 therapy may mitigate (Friberg and Reese, 2017; Köhnke et al, 2015). These data support testing the combination of tarlatamab and AMG 404 in patients with SCLC.

Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the safety, tolerability, and recommended phase 2 dose of tarlatamab in combination with AMG 404	• Dose-limiting toxicities (DLTs), treatment-emergent and treatment-related adverse events, changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
Secondary	
• To evaluate anti-tumor activity of tarlatamab in combination with AMG 404	• Objective response (OR) per modified response evaluation criteria in solid tumors (RECIST) v1.1, duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).
• To characterize the pharmacokinetics (PK) of tarlatamab in combination with AMG 404	• PK parameters including, but not limited to, maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), and area under the concentration-time curve (AUC) over the dosing interval

Overall Design

This is a phase 1b, multicenter, open-label study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of tarlatamab in combination with AMG 404 in subjects with SCLC. The study will consist of dose exploration (Part 1) and dose expansion (Part 2).

[redacted]

Part 1 (Dose Exploration)

The dose exploration part of the study will estimate the recommended phase 2 dose (RP2D) of tarlatamab in combination with AMG 404 using a modified toxicity probability interval (mTPI-2) design. A combination RP2D may be identified based on emerging safety, efficacy, and pharmacodynamic data prior to reaching a **maximum tolerated dose (**MTD**)**.

Part 2 (Dose Expansion)

Upon completion of Part 1 of the study, enrollment will commence in Part 2 to confirm the safety and tolerability of the selected dose and to further evaluate the efficacy of tarlatamab in combination with AMG 404.

Number of Subjects

Study enrollment ended in [redacted] A total of [redacted] subjects were enrolled in this study including [redacted] subjects in Part 1, and [redacted] subjects in Part 2.

Summary of Subject Eligibility Criteria

Adult subjects (≥ 18 years of age) with SCLC are eligible to enroll. Subjects must have histologically or cytologically confirmed SCLC and have progressed or recurred following at least 1 platinum-based regimen. Subjects must have measurable disease per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1, and adequate organ function (refer to inclusion criteria 107).

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. Tarlatamab will be administered as a short-term intravenous (IV) infusion (approximately 60 minutes [± 10 minutes] followed by a flush) on [redacted] in a [redacted] cycle beginning in cycle 2. The starting dose of tarlatamab will be a target dose of [redacted] mg with 1-step dosing. The highest planned target dose of tarlatamab will not exceed [redacted] mg using [redacted] regimen (see Section 4.1 for details on the starting dose). To reduce the risk of cytokine release

syndrome (CRS), premedication with dexamethasone [redacted] mg IV (or equivalent dose of other corticosteroids) will be administered within 1 hour prior to all cycle 1 doses. Intravenous hydration (1L normal saline over 4 to 5 hours) will also be administered following administration of tarlatamab in cycle 1. In addition, 1-step-dosing will be implemented in cycle 1 with [redacted] mg administered on cycle 1 [redacted] Sites are required to have tocilizumab or siltuximab (if tocilizumab not available) on site for potential treatment of CRS.

AMG 404 is an Amgen investigational product used in this study. AMG 404 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. AMG 404 will be administered as a short-term IV infusion (30 minutes [± 5 minutes]) [redacted] (± 3 days) at a dose of [redacted] mg (note if AMG 404 is initially administered on cycle 1 [redacted] there will be a [redacted] interval between the [redacted] mg cycle 1 [redacted] and [redacted] mg cycle 2-[redacted] dose). Since treatment initiation with tarlatamab may result in CRS, the first dose of AMG 404 will be administered on either [redacted] in cycle 1, and subsequently [redacted] ([redacted] beginning on cycle 2 [redacted] or cycle 2 [redacted]

Statistical Considerations

A total of approximately [redacted] subjects were anticipated to be enrolled in the study (up to [redacted] subjects in a dose exploration phase and the remaining subjects enrolled in a dose expansion phase). Up to [redacted] planned dose cohorts may be examined during dose exploration. Each cohort will enroll [redacted] subjects. Additional subjects can be enrolled if more data are needed. Up to [redacted] subjects can be enrolled in dose exploration part. At least [redacted] DLT- evaluable subjects need to be treated at a selected dose level. For the Dose Exploration phase, the sample sizes are empirically decided and consistent with conventional early oncology studies with the objective to estimate the RP2D and to evaluate safety and tolerability. Formal safety interim analyses will be performed for every [redacted] subjects who have had opportunity to have at least [redacted] of follow up since first dose of tarlatamab. If the sample size in the dose expansion phase of 10 (or 20), there is 65% (88%) probability of observing at least 1 adverse event with 10% incidence rate and the exact 95% confidence interval for 20% objective response (OR) is 3% to 56% (6% to 44%). Study enrollment ended in [redacted]. A total of [redacted] subjects were enrolled including [redacted] subjects in Part 1, and [redacted] subjects in Part 2.

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

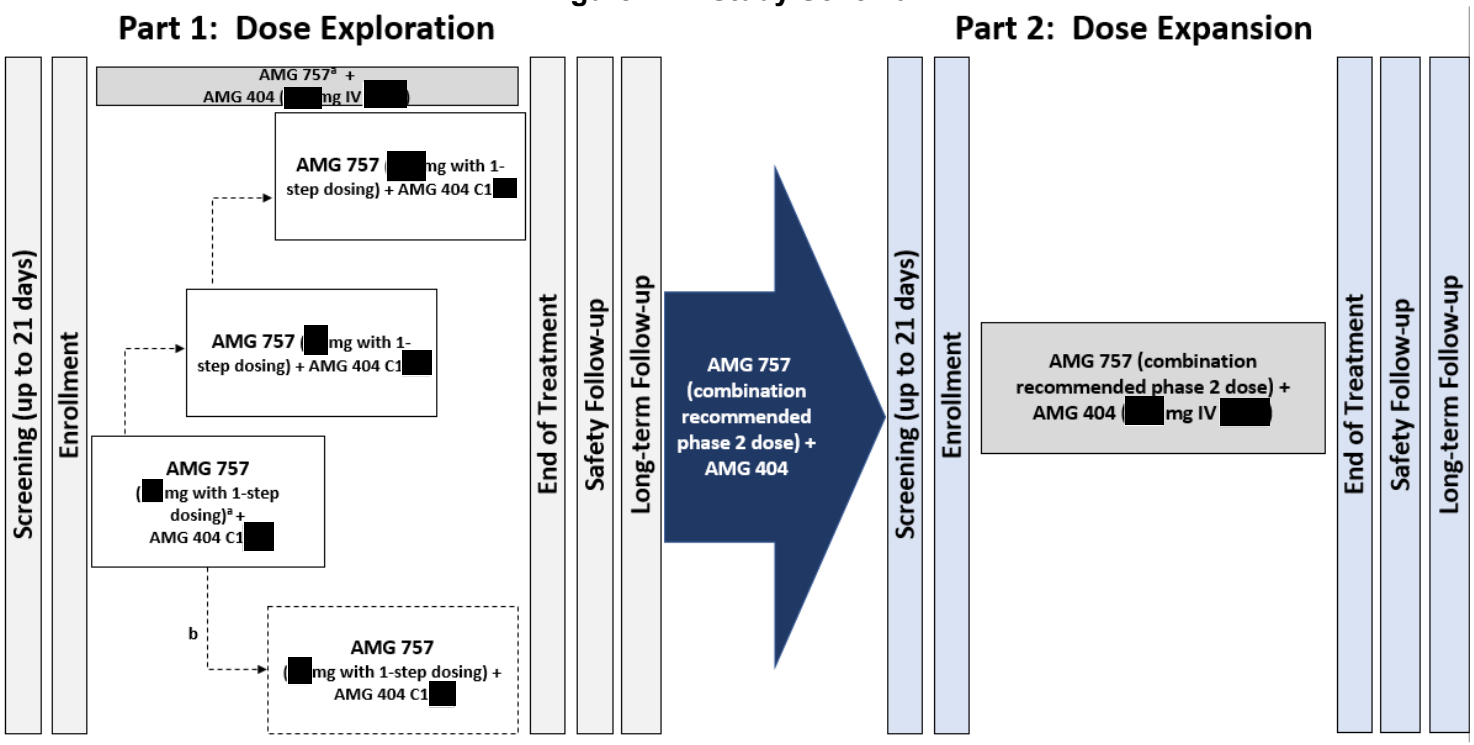
Statistical Hypotheses

No formal statistical hypotheses will be tested.

Sponsor Name: Amgen, Inc.

1.2 Study Schema

Figure 1-1. Study Schema[c]



C = cycle; DLT = dose level toxicity; FIH = first-in-human; IV = intravenous; PD = pharmacodynamics; Ph1 = phase 1; PK = pharmacokinetics;

[a] The starting dose and associated dosing schedule of tarlatamab will be a target dose of mg with 1-step dosing

[b] If the combination is not tolerated (based on target DLT rate > 30%), AMG 404 may be administered on cycle 1 Based upon emerging PK, PD, and safety data in the current study as well as the ongoing FIH study (20160323), alternative (intermediate) dose cohort levels, as part of the de-escalation recommendations may be explored (see Section 4.1 and Figure 4-1 for study design details pertaining to footnote b)

Study Periods:

- Screening: up to before enrollment
- Treatment: treatment continues until confirmed radiographic progression or disease progression*
- End of treatment: should occur as soon as possible (within) after the last dose of investigational product
- Safety follow-up: approximately after the end of the last dose of tarlatamab and approximately days after the last dose of AMG 404
- Long-term follow-up: every 3 months (± 2 weeks) up to 1 year 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

*Note: Subjects with confirmed disease progression per modified RECIST 1.1 criteria who have clinical benefit in the investigator's judgment may be allowed to continue treatment after approval by the Medical Monitor as per Section 7.2.

1.3 Schedule of Activities (SoA)

Table 1-1. Summary of Single Step Dosing Schedule of Tarlatamab to Mitigate Cytokine Release Syndrome (CRS) During Cycle 1

Tarlatamab Step Dosing	[redacted]			
One-step	First step dose	N/A	Step dose (equal to Target dose)	Target dose

N/A = not applicable

[redacted]

Table 1-2. Schedule of Activities: Tarlatamab Monotherapy

STUDY PERIOD/ TREATMENT CYCLE	Every Cycle[bb]				Every Other Cycle		EOT[ii]	SFU-1[ee,hh]	SFU-2[ff,hh]	LTFU[aa]
WEEK[b]	1		3		1					
DAY[b]	[redacted]									
HOUR (relative to infusion)[d]	Pre 757	EOI 757	Pre 757	EOI 757	Pre 757	EOI 757				
General/Safety Assessments										
Clinical Evaluation[e]	X		X				X	X	X	
Vital signs, pulse ox[f]	X		X				X	X	X	
12-lead ECG[g]	X[cc]		X[cc]							
ECHO or MUGA										
Adverse event review	←==========							==========→		
Serious adverse event review	←==========							==========→		
Prior/concomitant medication	←==========							==========→		
Local Laboratory Assessments										
CBC with differential	X		X				X	X	X	
Coagulation	X						X	X	X	
Chemistry panel[h]	X		X				X	X	X	
Lipase and Amylase	X							X		
Urinalysis					X					
Serum/urine pregnancy Test[i]	X							X	X	
Safety endocrine panel[j]	X						X	X		
CRP	X						X	X		
Ferritin	X						X	X		
Central and Biomarker Laboratory Tests	[redacted]									
Study Drug Administration										
Tarlatamab IV infusion[t]	[redacted]									
Hospital stay[w]										
MRI Brain[x]										
Radiological imaging and tumor burden assessment[y]					X		X[z]	X[z]		X[dd]
Survival Status and subsequent cancer therapy[aa]										X

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Abbreviations used: 0 = Hour zero; when Tarlatamab is infused; ACTH = adrenocorticotropic hormone; BP = blood pressure; C = cycle; C1 = cycle 1 CBC = complete blood count; CNS = central nervous system; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOI = end of infusion; EOT = end of treatment; FFPE = formalin-fixed paraffin-embedded; FSH = follicle stimulating hormone; FT4 = free thyroxine; HBcAb = anti-hepatitis B antibody; HBsAg = hepatitis B antigen; HCV = hepatitis C; HIV = human immunodeficiency virus; HR = heart rate; IGF-1 = insulin-like growth factor 1; IV = intravenous; LH = luteinizing hormone; MUGA = multigated acquisition; LDH = lactate dehydrogenase; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetic; Pre = pre-infusion; Q cyc = every cycle; Q2 Cyc = every 2 cycles; RECIST = response evaluation criteria in solid tumors; RR = respiratory rate; SCR = screening; SFU = safety follow-up; SOI = start of infusion; TLS = tumor lysis syndrome; TSH = thyroid stimulating hormone

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

b Each visit week and day is relative to of each cycle. Cycle 1 and 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 See Section 6.2.1.3 for more details regarding Step Dosing.

d
- End of infusion (EOI) assessments or procedures are to be completed immediately after infusion of tarlatamab. EOI indicates the time when the investigational product 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 dosing where laboratory assessments that were done within 48 hours prior to infusion do not need to be repeated).
- All assessments and procedures should be collected at the exact nominal time point as noted in the Schedule of Assessments. 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.

e Clinical evaluation including physical exam, ECOG, weight and neurological exams, writing test, and mini-mental status exams (neurology specialty consultation service as clinically indicated). Mini mental status exams and writing test are required on days clinical evaluation required per dosing regimen), (may be performed if clinically indicated on days) in cycle 1. Mini mental status exam and writing test may be performed in cycle 2 and beyond at the investigator's discretion. Performed at screening only: demographics, medical history, and height. Clinical evaluation should be completed within 6 hours prior to the first dose of tarlatamab.

f Vital signs (BP, HR, RR, temp) and pulse oximetry will be assessed. Vitals will be taken pre-AMG 404 infusion and at AMG 404 EOI. . For each tarlatamab-infusion for the first 2 cycles (during the hospitalization period) vital signs should be assessed as detailed in Section 8.4.1.

g ECGs will be collected once and considered safety ECGs. ECGs should be collected prior to blood draws when assessments are conducted at the same nominal time point (pre-infusion timepoints for tarlatamab and AMG 404 may be collected 15 minutes prior to infusion, post-infusion time points for tarlatamab may be collected ± 15 minutes of indicated time point). See Section 8.4.5.

h For cycles 1 and 2 only, please collect LDH, phosphorus, and uric acid along with the chemistry panel for TLS monitoring.

i Serum pregnancy test at screening; serum or urine pregnancy test monthly until from the last investigational product (tarlatamab or AMG 404) dose. Additionally, a pregnancy test at after last dose of AMG 404.

j Safety endocrine panels: ACTH, cortisol, TSH, and FT4 will be evaluated at screening, of every cycle starting with cycle 2, EOT, and SFU-1. Prolactin, FSH, LH, testosterone (in males) and estradiol (in females) will be evaluated only at screening, EOT, and as clinically indicated.

m A tumor biopsy is required at screening if patient has received any treatment prior to participating into this study and biopsy can be performed safely as determined by the investigators. Tumor tissue (archival or fresh biopsy) must be available. Subjects must consent to allow the acquisition of FFPE material (block or unstained slides) by study personnel.

[redacted]

r AMG 404 PK samples to be collected at pre-infusion and end of infusion in cycles 3, 5, 7, 9, and 11 and at pre-infusion in cycles 4, 6, 8, 10, and 12.

[redacted]

u Dexamethasone [redacted] mg IV (or equivalent dose of other corticosteroids) will be administered within 1 hour prior to all tarlatamab doses, in week 1 and step doses of tarlatamab in cycle 1 only.

v Refer to Section 6.1.4 for administration details.

[redacted]

x All subjects must have MRI/CT of the brain performed within [redacted] 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.

y
- [redacted]
- Tumor burden assessments will be performed based on modified RECIST 1.1 guidelines (see Section 11.9). [redacted]

z [redacted]

aa LTFU will be conducted every 3 months (± 2 weeks) for 1 year 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 only. If the investigator becomes aware of serious adverse events suspected to be related to investigational product or any fatal adverse event (regardless of causality) after the protocol-required reporting period (as defined in Section 8.4.9.1.3) is complete, 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 Event eCRF.

bb Assessments to be completed at specified timepoint beginning with cycle 3 and at each subsequent cycle unless otherwise specified.

cc For cycles 3 and 4 only: please collect ECG post-tarlatamab infusion. No further ECG's are collected after cycle 4.

dd For subjects who discontinued treatment for any reason other than confirmed PD, every effort should be made to perform radiographic imaging (CT/MRI) of the chest, abdomen, pelvis, and all other known sites of disease every 3 months until documentation of confirmed PD per modified RECIST 1.1, clinical progression, start of new anticancer therapy, or up to 12 months after the first dose of tarlatamab, whichever occurs first.

ee The first safety follow-up visit should be completed [redacted] from the last dose (tarlatamab or AMG 404).

ff The second safety follow-up visit should be completed [redacted] after the last dose of AMG 404 or prior to initiation of other therapy, whichever occurs first.

[redacted]

hh Subjects who discontinue AMG 404 but remain on treatment with AMG 757 will continue to have safety event collection at regularly scheduled study visits. The second safety follow-up visit need only occur if [redacted] has not elapsed from the end of AMG 404 treatment at the time of end of study treatment.

ii After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.9.1.3 for additional details.

2. Introduction

2.1 Study Rationale

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 (Owen et al, 2019). Tarlatamab is a half-life extended (HLE) bi-specific T-cell engager (BiTE®) molecule 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) Fc (fragment crystallizable; single chain fragment crystallizable [scFc]) region. Currently, tarlatamab is being evaluated in a phase 1 study (Study 20160323) of subjects with small cell lung cancer (SCLC).

AMG 404 is a fully human antibody that binds human programmed cell death-1 (PD-1) with high affinity and blocks the ability of this receptor to interact with its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). AMG 404 has been evaluated as a monotherapy agent in a phase 1 study (Study 20180143) of subjects with advanced or metastatic solid tumors.

Pembrolizumab (Keytruda®) and nivolumab (Opdivo®), both antibodies blocking human PD-1, were approved by the **United States food and drug administration (**US FDA**)** under the accelerated approval program for treatment of patients with metastatic SCLC who have progression after platinum-based chemotherapy and at least 1 other line of therapy (Keytruda® **United states prescribing information [**USPI**]**, 2020; Opdivo® USPI, 2019), based on relatively low response rates (19% with pembrolizumab and 12% with nivolumab; Keytruda® USPI, 2020; Opdivo® USPI, 2019). However, both approvals were subsequently withdrawn after confirmatory studies did not meet their primary endpoint of overall survival (OS) (Merck, 2021; Bristol Myers Squibb, 2020). These data suggest that immune checkpoint inhibition may need to be combined with other therapies in second line or later.

The combination of tarlatamab and anti-PD-1 antibodies increases T-cell mediated redirected lysis of tumor cells that express DLL3 in vitro as compared to tarlatamab alone. In addition, upregulation of PD-1/PD-L1 in the tumor microenvironment is a mechanism of resistance to BiTE® therapy that treatment with anti-PD-1 therapy may mitigate (Friberg and Reese, 2017; Köhnke et al, 2015). These data support testing the combination of tarlatamab and AMG 404 in patients with SCLC.

2.2 Background

2.2.1 Disease

Small cell lung cancer (SCLC), accounting for 10% to 15% of lung cancer (Rudin et al, 2015), is an aggressive lung cancer subtype with neuroendocrine differentiation and strongly associated with smoking (Koinis et al, 2016). It displays a distinct natural history characterized by a high growth fraction, rapid doubling time and early establishment of widespread metastatic lesions (Gustafsson et al, 2008). While 30% of patients present with disease confined to **1** hemithorax (limited disease [LD]), the majority of cases have disease not encompassed by one radiotherapy field (extensive disease [ED]). Small cell lung cancer is exquisitely sensitive to first-line chemotherapy (approximately 60% to 70% response rates) and to radiation which is stark contrast to subsequent resistance to second line and subsequent therapies after disease recurrence (Byers and Rudin, 2015). Patients with ED develop drug resistance and die as a result of disease at a median time of 10 to 12 months from diagnosis (Rudin et al, 2015). For patients with ED SCLC, first-line treatment is platinum-based chemotherapy. Most patients in the United States receive platinum-etoposide (EP) chemotherapy (with either carboplatin or cisplatin), and some patients receive platinum-irinotecan as an alternative, especially outside the United States. In March 2019, atezolizumab was approved by the US FDA in combination with carboplatin and etoposide for the first-line treatment of adult patients with ED-SCLC (TECENTRIQ® United States Prescribing Information [USPI], 2019). In March 2020, durvalumab, in combination with standard-of-care chemotherapy, etoposide, and carboplatin or cisplatin, was approved by the FDA as a frontline treatment for adult patients with extensive stage SCLC (IMFINZI® USPI). Similar approvals for these molecules have also now been received in **European union (**EU**)** and other geographic regions, although levels of adoption remain variable globally.

After relapse, topotecan is approved by the US FDA for relapses that occur after 45 days from the completion of chemotherapy. However, despite its indication in this setting, topotecan has produced disappointing response rates (Byers and Rudin, 2015). Based on the results of an open-label study of 105 patients with SCLC after failure of first-line therapy, lurbinectedin recently received accelerated approval by the US FDA following progression on or after platinum-based chemotherapy (Trigo et al, 2020).

2.2.2 Amgen Investigational Product Background: Tarlatamab

Tarlatamab (International Nonproprietary Name [INN]; AMG 757) is an HLE BiTE® antibody construct combining the binding specificities for DLL3 and CD3 genetically fused to the N-terminus of a single chain IgG Fc (fragment crystallizable; scFc) region and is being developed with the intent to treat patients with SCLC.

Refer to the specific section of the Investigator Brochure 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 Investigator's Brochure.

2.2.2.1 Pharmacology

The activity of tarlatamab requires the simultaneous binding to both target cells and T cells. The pharmacological effect of tarlatamab is mediated by specific redirection of previously primed cytotoxic CD8+ or CD4+ T lymphocytes to kill DLL3+ cells. Tarlatamab is a potent molecule showing mean half-maximal lysis of human tumor cell lines by human effector cells in vitro over a range of [redacted]

As part of the T cell activation process, BiTE® antibody constructs, such as tarlatamab, cause 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).

The subsequent release of the pore-forming protein perforin and the apoptosis-inducing proteolytic enzyme granzyme B by T cells results in the induction of apoptosis in the target cells.

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 [redacted]

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 [redacted]

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 a Good Laboratory Practice (GLP) compliant [redacted] cynomolgus monkey toxicology studies. In the [redacted] study, tarlatamab was administered once weekly by intravenous (IV) infusion at [redacted] and [redacted] μg/kg. Tarlatamab-related changes were limited to a minor decrease in lymphocyte populations (detected after the second dose only) at [redacted] μg/kg, a slightly increased heart rate (HR) (on [redacted] but not at [redacted]) at ≥ [redacted] μg/kg, and a minimal to mild mixed inflammatory cell infiltrate in the pituitary at [redacted] and [redacted] 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 [redacted] study, tarlatamab-related clinical pathology changes were limited to a minimal decrease in lymphocytes at [redacted] μg/kg. In addition, tarlatamab-related changes were observed in the pituitary gland at ≥ [redacted] 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 [redacted] μg/kg in both the [redacted] studies based on the absence of any tarlatamab-related adverse findings.

2.2.2.3 Background Clinical Experience With Tarlatamab

As of 29 September 2021 data cut, [redacted] subjects were enrolled in the tarlatamab first in human (FIH) Study 20160323, 120 (96.8%) of whom received at least 1 dose of tarlatamab. [redacted] subjects received monotherapy in Part A1 (cohorts 1 to 10, cohort 23, and cohort 26 in the dose exploration phase): 1 subject each was assigned [redacted] mg of tarlatamab; [redacted] subjects were assigned [redacted] mg; [redacted] subjects were assigned [redacted] mg; [redacted] subjects were assigned [redacted] mg (ie, [redacted] mg starting cycle 1 [redacted] after an initial step dose of [redacted] mg at cycle 1 [redacted] subjects were assigned [redacted] mg; [redacted] subjects were assigned [redacted] mg; [redacted] subjects were assigned [redacted] mg; [redacted] subjects were assigned [redacted] mg (ie, [redacted] mg starting cycle 1 [redacted]

following **2-**step dose of [redacted] mg at cycle 1 [redacted] and [redacted] mg at cycle 1 [redacted] of tarlatamab monotherapy administered IV [redacted]; and [redacted] subjects were assigned [redacted] mg of extended IV dosing. Overall, all subjects (100%) in Part A1 had treatment-emergent adverse events; the most commonly reported adverse events were cytokine release syndrome (CRS) ([redacted] subjects [44.4%]); pyrexia ([redacted] subjects [33.3%]); fatigue ([redacted] subjects [28.4%]); constipation ([redacted] subjects [24.7%]); nausea ([redacted] subjects [25.9%]); decrease appetite ([redacted] subjects [23.5%]); anaemia and headache ([redacted] subjects [17.3%]); and dysgeusia ([redacted] subjects [19.8%]). Serious adverse events were reported for [redacted] subjects (49.4%), treatment-related adverse events leading to withdrawal from tarlatamab were reported for [redacted] subjects (3.7%), and grade ≥ 3 treatment-emergent adverse events were reported for [redacted] subjects (53.1%). [redacted] subject (1.2%), who received 2 doses of tarlatamab at [redacted] mg IV [redacted] had a treatment-emergent fatal adverse event of pneumonitis, which was considered to be a dose-limiting toxicity (DLT) event.

Among subjects who received tarlatamab in Part A1 (ie, cohorts 1 to 10, cohort 23, and cohort 26), CRS is the most frequently reported adverse event occurring in [redacted] subjects (44.4%) with grade ≥ 2 CRS occurring in [redacted] subjects (9.9%) and grade ≥ 3 CRS occurring in [redacted] subject (1.2%). No grade 4 or higher CRS has been reported at the time of the data cutoff date. Cytokine release syndrome presented mainly as fever, tachycardia, nausea, and fatigue ± hypotension and was reversible. In [redacted] subjects (13.6%), CRS was reported as a serious adverse event, 1 event of which led to treatment discontinuation. Cytokine release syndrome 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.

As of 29 September 2021, preliminary efficacy data was available for [redacted] subjects who received monotherapy in Part A1. Overall, a confirmed partial response (PR) was observed starting at a dose level of [redacted] through [redacted] mg in a total of [redacted] subjects for an overall **objective response rate** (95% CI) of 19.5% (11.3, 30.1). The disease control rate (95% CI) was 49.4% (37.8, 61.0).

As of 29 September 2021, data cut, [redacted] subjects (100.0%) receiving monotherapy in Part A2 (ie, cohort 30) had treatment-emergent events. Grade ≥ 3 adverse events were reported in [redacted] subjects (35.3%). Serious adverse events were reported in [redacted] subjects (52.9%). No adverse events were fatal or led to discontinuation of tarlatamab. Adverse

events by preferred term reported for ≥ 20.0% of subjects were CRS ([redacted] subjects [76.5%]); dysgeusia and pyrexia (each [redacted] subjects [47.1%]); decreased appetite, headache, and vomiting (each [redacted] subjects [29.4%]); and arthralgia, fatigue, and nausea (each [redacted] subjects [23.5%]).

Among subjects who received tarlatamab in Part A2, CRS was grade ≥ 2 in [redacted] subjects (11.8%); no grade ≥ 3 events were reported. In [redacted] subjects (41.2%), CRS was reported as a serious adverse event. No CRS (AMQN) adverse events were fatal or led to discontinuation of tarlatamab.

Neutropenia was grade ≥ 2 in [redacted] subjects (23.5%) and grade ≥ 3 in [redacted] subjects (11.8%). Neutropenia was reported as a serious adverse event in [redacted] subject (5.9%). No neutropenia adverse events were fatal or led to discontinuation of tarlatamab.

As of the data cut-off, [redacted] subjects received [redacted] in Part C of the ongoing FIH Study 20160323 with [redacted] subjects assigned [redacted] mg and [redacted] subjects assigned [redacted] mg of tarlatamab. Cohort 16 with [redacted] mg of tarlatamab administered over 1-hour [redacted] in [redacted] administered at [redacted] mg [redacted] has been deemed safe and tolerable by the dose level review team (DLRT). As of 29 September 2021, [redacted] (100%) subjects had treatment-emergent adverse events, [redacted] (37.5%) subjects had serious treatment-emergent adverse events, [redacted] (37.5%) subjects had grade ≥ 3 treatment-emergent adverse events, [redacted] (0%) subjects had treatment-emergent adverse events that led to treatment discontinuation. The most common adverse events include: fatigue ([redacted] subjects [62.5%]), nausea ([redacted] subjects [37.5%]), decreased appetite ([redacted] subjects [37.5%]), vomiting ([redacted] subjects [37.5%]), constipation ([redacted] subjects [25%]), contusion ([redacted] subjects [25%]), dyspnea ([redacted] subjects [25.0%]), headache ([redacted] subjects [25%]), myalgia ([redacted] subjects [25.0%]), and pyrexia ([redacted] subjects [25%]). Cytokine release syndrome was reported in [redacted] subject (12.5%); the event was grade 2, nonserious, and did not lead to discontinuation of treatment.

[redacted] subjects received a CRS mitigation strategy in Part D of the ongoing FIH Study 20160323 consisting of [redacted] mg tarlatamab plus dexamethasone. All [redacted] subjects (100.0%) reported a treatment-emergent adverse event. Grade ≥ 3 adverse events were reported for [redacted] subjects (57.1%). A fatal adverse event was reported in [redacted] subject (7.1%); the preferred term was small cell lung cancer. Adverse events by preferred term reported for ≥ 20.0% of subjects were CRS ([redacted] subjects [64.3%]), pyrexia

(subjects [50.0%]), dysgeusia (subjects [42.9%]), constipation (subjects [35.7%]), and fatigue, headache, hypomagnesemia, hypotension, and nausea (each subjects [21.4%]). Reported CRS of grade ≥ 2 was reported in subjects (28.6%). No grade ≥ 3 CRS adverse events were reported. Serious CRS was reported in subjects (28.6%). Cytokine release syndrome led to discontinuation of tarlatamab in subject (7.1%).

As of 29 September 2021, with a total of subjects (subjects in Study 20160323, subject in Study 2020040, and subject in Study 20200439) exposed to tarlatamab, grade ≥ 2 neutropenia was observed in subjects (11.7%), and subjects (4.1%) experienced grade 4 or higher neutropenia events. There were no fatal neutropenia events. Serious adverse events of neutropenia were reported for subjects (1.7%). tarlatamab was interrupted in subjects (3.3%) due to neutropenia and discontinued in subjects (1.7%) (interrupted in subject prior to discontinuation). There were no cases of febrile neutropenia.

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

Within the evaluated target dose range of mg (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 . Approximate steady state in serum tarlatamab exposures was achieved within 4 weeks of every other week target regimen initiation.

Refer to the AMG 757 Investigator's Brochure for additional information.

2.2.3 Amgen Investigational Product Background: AMG 404

2.2.3.1 Nonclinical Pharmacology

AMG 404 is a fully human antibody that binds human and cynomolgus monkey PD-1 with high affinity and blocks the ability of these receptors to interact with human ligands, PD-L1 and PD-L2. The ligand blocking activity of AMG 404 was evaluated in 3 different assays using 3 different readouts and both cell-expressed, as well as recombinant, soluble ligands. In each assay, AMG 404 demonstrated the expected dose-dependent activity, indicating it is a potent inhibitor of human and cynomolgus monkey PD-1 binding.

AMG 404 blocks the interaction between cynomolgus monkey PD-1 and human PD-L1 with a similar half maximal inhibitory concentration (IC_{50}) as human PD-1 and human

PD-L1, suggesting that cynomolgus monkey is an appropriate species for nonclinical safety evaluation.

AMG 404 is an IgG1 antibody; however, the Fc region has been modified to eliminate undesired interactions with Fc gamma receptors. The absence of Fc-binding to Fc gamma receptors was demonstrated in a functional assay where AMG 404 induced little to no antibody-dependent cellular cytotoxicity (ADCC) as compared to a positive control anti-CD38 antibody. These results demonstrate that the Fc region of AMG 404 does not interact with Fc gamma receptors.

2.2.3.2 Toxicology

The potential for AMG 404 to cause acute release of cytokines from human peripheral blood leukocytes (PBL) in the presence of human endothelial cells (HUVECs) was evaluated in vitro. Human PBL were cultured in autologous Platelet Poor Plasma (PPP) in the presence of HUVECs with AMG 404 ([redacted] µg/mL) for 24 hours, and supernatants from the cultures were subsequently assessed for the presence of cytokines (IFNγ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 p70, and TNFα). Under the conditions tested in this assay, AMG 404 did not induce cytokine release above background levels.

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

reaction to the administration of an exogenous protein. In conclusion, administration of AMG 404 by once weekly IV bolus or SC injection was well tolerated in cynomolgus monkeys at levels of [redacted] mg/kg IV and [redacted] mg/kg IV and SC.

2.2.3.3 Nonclinical Pharmacokinetics

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

The toxicokinetics of AMG 404 were characterized in a GLP study after weekly IV administration of [redacted] or [redacted] mg/kg or SC administration of [redacted] mg/kg for 4 consecutive weeks. Following repeat dose administration, AMG 404 exposure increased approximately dose-proportionally from [redacted] to [redacted] mg/kg as measured by maximum serum concentration (C_{max}) and area under the concentration-time curve (AUC) over [redacted] days. AMG 404 exposures were similar between male and female animals.

2.2.3.4 Clinical Experience

As of the 30 April 2021 data cutoff date, preliminary safety data were available for [redacted] subjects with advanced or metastatic solid tumors who had received at least 1 dose of AMG 404 IV [redacted] in monotherapy Study 20180143. These subjects were dosed at 1 of 3 dose levels: [redacted] subjects were dosed at the [redacted] mg dose level, [redacted] subjects at the [redacted] mg dose level, and [redacted] subjects at the [redacted] mg [redacted] dose level (the highest dose level studied to date).

Among the [redacted] subjects treated with at least 1 dose of AMG 404 in Study 20180143, the treatment emergent adverse events, any grade, with a subject incidence of at least 10% by preferred term were: fatigue (n = [redacted] 33.8%), nausea (n = [redacted] 26.9%), decreased appetite (n = [redacted] 23.1%), vomiting (n = [redacted] 16.9%), pyrexia (n = [redacted] 16.2%), diarrhea (n = [redacted] 15.4%), constipation (n = [redacted] 14.6%), anemia (n = [redacted] 13.8%), arthralgia, abdominal pain, and rash (n = [redacted] 11.5% each), and aspartate aminotransferase increased, hypothyroidism, and dyspnea (n = [redacted] 10.0% each). Treatment-emergent adverse events with a worst grade ≥ 3, with a subject incidence of at least 2 were: anemia (n = [redacted] 5.4%), sepsis (n = [redacted] 3.8%), fatigue (n = [redacted] 3.1%), seizure (n = [redacted] 2.3%), and abdominal pain, aspartate aminotransferase increased, back pain, decreased appetite, disease progression, dyspnea, hyponatremia, postoperative wound infection,

urinary tract infection, colorectal cancer metastatic, metastases to spine, malignant neoplasm of thymus, and pancreatic cancer (n = [redacted] 1.5% each). In [redacted] subjects (6.2%), reported treatment emergent adverse events led to AMG 404 discontinuation and the adverse events were: brain edema, diarrhea, dysarthria, hemorrhage, immune-mediated enterocolitis, malignant neoplasm of thymus, porocarcinoma, and tumor hemorrhage (n = [redacted] 0.8% each). [redacted] subjects reported treatment emergent fatal adverse events, of which [redacted] (11.5%) came under the System Organ Class, neoplasms benign, malignant, and unspecified (incl cysts and polyps) and the remaining 4 treatment emergent fatal adverse events were: disease progression, coronavirus disease 2019 (COVID-19), hemorrhage, and (uncoded) recurrent undifferentiated hepatic sarcoma (n = [redacted] 0.8% each).

Hypothyroidism, colitis, and myasthenia gravis are identified adverse drug reactions (ADRs) to AMG 404. In Study 20180143, administration of AMG 404 has been associated with the reported events of hypothyroidism ([redacted] subjects [10.0%], all subjects experienced an event grade ≤ 2) or blood thyroid stimulating hormone (TSH) increased ([redacted] subjects [3.1%], [redacted] subject experienced a grade 3 event, [redacted] subjects experienced a grade ≤ 2 event). In total, [redacted] subjects (13.1%) experienced an event associated with an underactive thyroid. [redacted] hypothyroidism event was serious. No event of hypothyroidism or blood TSH increased led to AMG 404 discontinuation. Administration of AMG 404 has been associated with noninfectious colitis in [redacted] subjects (1.5%). [redacted] subject experienced the adverse events colitis (grade 2, nonserious), immune-mediated enterocolitis (grade 3, serious), and diarrhea (grade 2, nonserious). The [redacted] subject experienced the adverse event immune-mediated enterocolitis (grade 2, nonserious). Both subjects with noninfectious colitis discontinued AMG 404 due to colitis/diarrhea. Administration of AMG 404 has been associated with the serious adverse event myasthenia gravis in [redacted] subject. This was a study subject in a phase 1b/2 combination study of AMG 404 and [redacted] (Study 20190505 Subprotocol C). Both study drugs were permanently discontinued because of the event. As of 30 April 2021, [redacted] study subjects had been exposed to this investigational product combination. The myasthenia gravis event was reported in [redacted] subject, between the ages of 60 and 70 years, with stage 4 prostate cancer.

As of 30 April 2021, preliminary efficacy data were available for [redacted] subjects dosed with AMG 404 who had an objective response value recorded. Among all cohorts, [redacted] subjects (9.5%) had a confirmed partial response, and [redacted] subjects (43.1%) had stable

disease. Among cohorts 6, 7, 8, and 9, there were [redacted] subjects with a response value who were dosed with AMG 404 [redacted] mg IV [redacted] Of these [redacted] subjects, [redacted] subjects (13.4%) had a confirmed partial response, and [redacted] subjects (44.8%) had stable disease.

Refer to the AMG 404 Investigator's Brochure for additional information.

2.3 Benefit/Risk Assessment

2.3.1 Therapeutic Context

The combination of tarlatamab and AMG 404 will be investigated in subjects with SCLC.

2.3.2 Key Benefits

Key benefits of the combination of tarlatamab and AMG 404 will be investigated and will be described when the data become available. Potential benefits include reduction or regression of SCLC disease burden.

2.3.3 Key Safety Information

2.3.3.1 Tarlatamab

Based on experience with tarlatamab in the phase 1 FIH Study 20160323 for the indication of SCLC, the key safety information for tarlatamab includes CRS and neutropenia as identified risks. The additional potential safety concerns of neurological events, pituitary dysfunction**,** and tumor lysis syndrome (TLS) are summarized in the sections below and are based on the biological mechanism of action, experience with other BiTE® molecules, and on the potential for on target, off-tumor effect.

Table 2-1. Key Safety Risk of Tarlatamab

Safety Risk	Description
CRS	CRS is an adverse drug reaction of tarlatamab administration based on safety data from tarlatamab phase 1 FIH 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 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 • Neurologic: headache, mental status changes, confusion, delirium, world finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures • Respiratory: dyspnea, tachypnea, hypoxemia • Skin: rash • Gastrointestinal: nausea, vomiting, diarrhea • 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. Specific recommendations for the management of CRS, and infusion interruption and stopping rules are found in Table 6-4
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 6-8**.

ALL = acute lymphoblastic leukemia; BiTE® = bi-specific T-cell engager; CD-19 = cluster of differentiation 19; CRS = cytokine release syndrome; FIH = first-in-human; GLP = Good Laboratory Practices; SCLC = small cell lung cancer

2.3.3.1.1 Additional Potential Safety Concerns for Tarlatamab

2.3.3.1.1.1 Neurological Events

There exists the risk of neurotoxicity with administration of tarlatamab. 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 tarlatamab administration in the tarlatamab phase 1 FIH Study 20160323 for the indication SCLC. No neurologic events were observed in the tarlatamab [redacted] GLP toxicology studies in cynomolgus monkeys.

2.3.3.1.1.2 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

For this trial, Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) will be defined according to the criteria referenced in the publication by Lee et al (2019). While the grading system has been developed in large part from chimeric antigen receptor T cells (CAR-T) therapies, symptoms of ICANS may be shared among immune effector cell-associated therapies such as BiTE® molecules.

Refer to Section 6.8.2 for details on specific guidance for ICANS.

2.3.3.1.1.3 Pituitary Dysfunction

There exists the risk of pituitary dysfunction with administration of tarlatamab. The target DLL3 protein is expressed in the pituitary and there were observations of a tarlatamab related mixed inflammatory cell infiltrate in the pituitary in the [redacted] GLP cynomolgus monkey toxicology studies.

2.3.3.1.1.4 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.

2.3.3.2 AMG 404

AMG 404 has been evaluated as a monotherapy agent in a FIH, phase 1 study (Study 20180143) of subjects with advanced or metastatic solid tumors. Based on the

available clinical data with AMG 404, hypothyroidism, colitis, and myasthenia gravis are identified risks of AMG 404. (Table 2-2).

Table 2-2. Key Safety Risks of AMG 404

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

2.3.3.2.1 AMG 404 Potential Safety Concerns

Additional key safety information (Table 2-3), which are based on the mechanism of action, the nonclinical safety pharmacology and toxicology studies for AMG 404, available data from the ongoing clinical study, and class effects of approved anti-PD-1/PD-L1 checkpoint inhibitors, but for which a causal association with AMG 404 has not been established, are summarized below.

Table 2-3. Potential Safety Concerns Based on Drug Class Effects, Biological Mechanism of Action, and Nonclinical Studies

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

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

Clinical signs and symptoms of immune-related toxicities and infusion-related reactions, along with safety laboratory parameters, will be monitored during the study to ensure subjects' safety. To mitigate embryofetal toxicity risk, study subject contraception will be required, and pregnancy status will be monitored. Refer to Section 6.2.2.2.1 for specific recommendations regarding the mitigation and management of immune-related toxicities and infusion-related reactions.

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

2.3.3.3 Key Risks for Tarlatamab in Combination with AMG 404

To date, there is limited safety data with BiTE® molecules in combination with PD-1 inhibitors. However, in a phase 1 study, the combination of the BiTE® molecule blinatumomab with the PD-1 inhibitor nivolumab was reported to be safe and tolerable in a small number of subjects with ALL (Webster et al, 2018). No clinical or preclinical safety information is available for the combination of tarlatamab with AMG 404. In the ongoing tarlatamab FIH study (20160323), a [redacted] being conducted (tarlatamab dose level of [redacted] mg in [redacted] deemed safe and tolerable). Based on biological mechanism of action and initial clinical safety information from the monotherapy study with tarlatamab (20160323), the key safety information and additional risks described for monotherapy would also be expected along with the key risks described for AMG 404. Moreover, with

combination treatment, adverse events may be more severe and occur at different time points and/or dose levels in comparison to monotherapy. In particular, synergistic activation of T cells is expected and may contribute to more severe immune-related toxicities. Pneumonitis is an immune mediated toxicity for the PD-1 inhibitor class of drugs and has been observed in tarlatamab. Refer to Section 6.8 for specific recommendations regarding the mitigation and management of CRS and infusion-related reactions. Key safety risks for the combination of tarlatamab and AMG 404 include:

- exacerbated CRS and/or infusion reactions
- exacerbated pituitary dysfunction
- exacerbated neurologic events

The available data thus far with BiTE® molecules in combination with anti-PD-1 suggests that the combination is tolerable. Additionally, given the overall low incidence of grade 2 or higher CRS (preferred term, 11%, with only 1 G3 CRS reported) with a reported incidence of grade 2 or higher CRS following cycle 1 [redacted] administration of 6% (preferred term) with tarlatamab monotherapy along with the low risk of reported infusion-related reactions (preferred term) reported thus far with AMG 404 monotherapy, the likelihood of the combination developing intolerable CRS or infusion-related reactions appears to be sufficiently low to merit the administration of both investigational products initially on cycle 1 [redacted] To further mitigate this risk, a 1-week stagger in enrollment of Subject 1 and Subject 2 in each dose cohort will take place to monitor for potential first dose effects associated with the combination therapy given on cycle 1 [redacted] If de-escalation is necessary, the study design incorporates the possibility that first dose effects, such as CRS, may be exacerbated with the combination on cycle 1 [redacted] by adjusting the dosing schedule to allow for AMG 404 to be administered initially on cycle 1 [redacted] or cycle 1 [redacted] based on emerging safety data and the recommendations of the dose level review meeting (DLRM).

Initially, subjects will be hospitalized after administration of tarlatamab and AMG 404 to monitor for these safety risks (refer to Section 8.1.2). Clinical signs and symptoms, along with safety laboratory parameters, will be monitored during study treatment cycles to ensure subjects' safety. Refer to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline 2019 for specific recommendations regarding the mitigation and management of immune-related toxicities.

3. Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• To evaluate the safety, tolerability, and recommended phase 2 dose of tarlatamab in combination with AMG 404	• Dose-limiting toxicities (DLTs), treatment-emergent and treatment-related adverse events, changes in vital signs, electrocardiograms (ECGs), and clinical laboratory tests
Secondary	
• To evaluate anti-tumor activity of tarlatamab in combination with AMG 404	• Objective response (OR) per modified response evaluation criteria in solid tumors (RECIST) v1.1, duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).
• To characterize the pharmacokinetics (PK) of tarlatamab in combination with AMG 404	• PK parameters including, but not limited to, maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), and area under the concentration-time curve (AUC) over the dosing interval
Exploratory	
[redacted]	

4. Study Design

4.1 Overall Design

This is a phase 1b, multicenter, open-label study evaluating the safety, tolerability, PK, pharmacodynamics (PD), and efficacy of tarlatamab in combination with AMG 404 in subjects with SCLC. The study will consist of dose exploration (Part 1) and dose

expansion (Part 2). Study enrollment ended in January 2023. A total of [redacted] subjects were enrolled including [redacted] subjects in Part 1, and [redacted] subjects in Part 2.

[redacted]

Part 1 (Dose Exploration):

The dose exploration part of the study will estimate the recommended phase 2 dose (RP2D) of tarlatamab in combination with AMG 404 using a modified toxicity probability interval (mTPI-2) design. A combination RP2D may be identified based on emerging safety, efficacy, and pharmacodynamic data prior to reaching an MTD.

AMG 404 will be administered (Table 6-1) as a short-term IV infusion (30 minutes) every [redacted] (± 3 days) (note if AMG 404 is initially administered on cycle 1 [redacted] there will be a [redacted] interval between the cycle 1 [redacted] and cycle 2 [redacted] dose). AMG 404 will be administered at the recommended phase 2 dose of [redacted] mg throughout the study. The starting dose of tarlatamab will be [redacted] mg with 1-step dosing ([redacted] mg on cycle 1 [redacted] followed by [redacted] mg on cycle 1 [redacted] [redacted] mg on cycle 1 [redacted] and [redacted] mg [redacted] thereafter). Thus far in the ongoing FIH study (Study 20160323), the highest target dose deemed safe and tolerable is [redacted] mg. Planned dose levels in Study 20160323 are shown in Table 4-1. The highest planned target dose of tarlatamab will not exceed [redacted] mg in this study using the [redacted] regimen.

Table 4-1. Planned Target Doses per Dose Cohort Level

Dose Cohort Levels	Dose (mg) IV [redacted]
-1	[redacted]
1	
2	
3	

IV = intravenous
Footnotes are referenced from first-in-human study (Study 20160323)

[redacted]

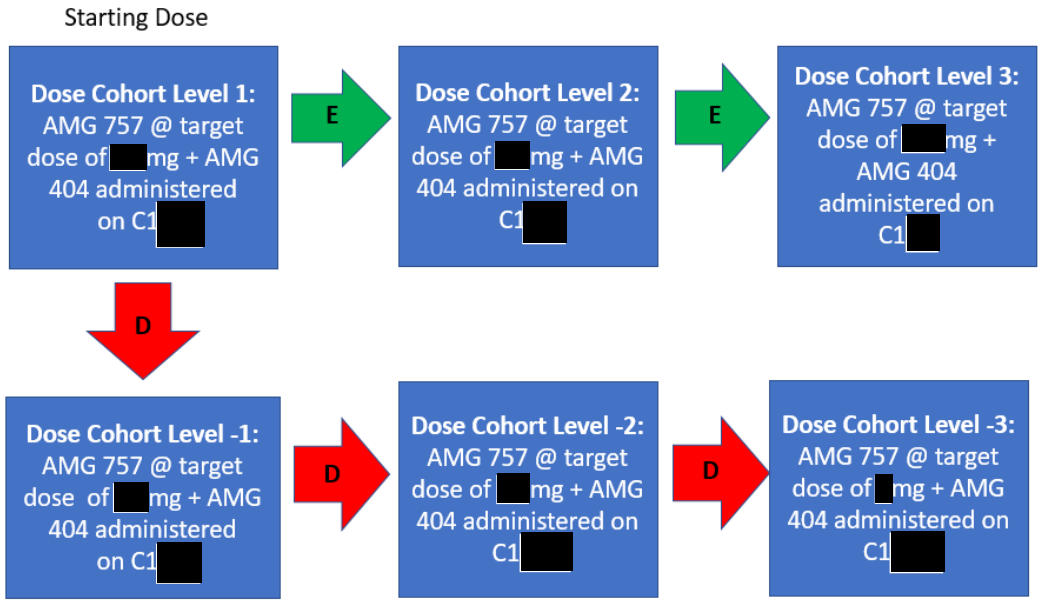
To mitigate the risk of CRS and to potentially optimize the PD activity of tarlatamab, a step dosing approach with 1-step dosing will be implemented as part of the dosing schedule. Based on emerging safety data and the recommendations of the DLRM, the dosing schedule may be adjusted to allow for AMG 404 to be administered initially on

cycle 1 [redacted] or cycle 1 [redacted]. Depending on which day AMG 404 is administered on in cycle 1, beginning in cycle 2, AMG 404 will be administered [redacted] beginning on cycle 2 [redacted] or cycle 2 [redacted] (see Table 11-8 and Table 11-9 for more details).

Part 1 may include one or more of the following planned dose levels of tarlatamab in combination with a fixed dose of AMG 404 (design in Figure 4-1):

- Dose Cohort Level 1: tarlatamab at a target dose of [redacted] mg administered IV [redacted] (with 1-step dosing) in combination with AMG 404 at [redacted] mg IV [redacted] ([redacted] beginning on cycle 1 [redacted]
- Dose Cohort Level 2: tarlatamab at a target dose of [redacted] mg administered IV [redacted] (with 1-step dosing) in combination with AMG 404 at [redacted] mg IV [redacted] beginning on cycle 1 [redacted]
- Dose Cohort Level 3: tarlatamab at a target dose of [redacted] mg administered IV [redacted] (with 1-step dosing) in combination with AMG 404 at [redacted] mg IV [redacted] beginning on cycle 1 [redacted]
- Dose Cohort Level -1: tarlatamab at a target dose of [redacted] mg administered IV [redacted] (with 1-step dosing) in combination with AMG 404 at [redacted] mg IV [redacted] (in case Dose Cohort Level 1 is not well tolerated) beginning on cycle 1 [redacted]
- Dose Cohort Level -2: tarlatamab at a target dose of [redacted] mg administered IV [redacted] (with 1-step dosing) in combination with AMG 404 at [redacted] mg IV [redacted] (in case Dose Cohort Level -1 is not well tolerated) beginning on cycle 1 [redacted]
- Dose Cohort Level -3: tarlatamab at a target dose of [redacted] mg administered IV [redacted] (with 1-step dosing) in combination with AMG 404 at [redacted] mg IV [redacted] (in case Dose Cohort Level -2 is not well tolerated) beginning on cycle 1 [redacted]

Figure 4-1. Part 1 Tarlatamab and AMG 404 Planned Dose Levels



D = de-escalation; E = escalation

Based upon emerging PK, PD, and safety data in the current study as well as the ongoing FIH study (20160323), alternative (intermediate) dose cohort levels, [redacted] as part of the de-escalation recommendations per the DLRM may be explored.

Step Dosing

Due to its known mechanism of action, subjects are at an increased risk for CRS during initiation of tarlatamab treatment. To mitigate this risk, tarlatamab will be administered with 1-step dosing. One-step dosing involves a first step dose on [redacted] mg), followed by a step dose on [redacted] (equal to the target dose) and the target dose on [redacted] then [redacted]

Dose exploration will begin with [redacted] subjects treated at Dose Cohort Level 1. The study DLT period is [redacted] Once all subjects enrolled at a certain Dose Cohort Level are DLT evaluable, a DLRT meeting will be convened. Depending on observed safety data, the following may occur: 1) dose de-escalation to the next lowest Dose Cohort Level, 2) additional enrollment to the current Dose Cohort Level, or 3) dose escalation to the next highest Dose Cohort Level or initiation of enrollment in Part 2. Re-escalation to the next higher Dose Level may be allowed, as appropriate. If re-escalation occurs, alternative (intermediate) dose levels may be explored per the recommendations of the

DLRM, [redacted].

Dose escalation/de-escalation recommendations will be guided by a mTPI-2 model (Guo et al, 2017) with a target toxicity probability of 30%, equivalence toxicity interval of (25%, 33%) and probability of overdosing of 95%. Beta (1, 1) is used as a prior distribution.

The detailed information of escalation/de-escalation rules are defined in Table 4-2. The DLT decision starts from the [redacted] subject.

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

Number of Evaluable Subjects	Number of DLTs	Decision
[redacted]	0	E
	1-2	D
	3	DU
	0	E
	1	S
	2	D
	≥ 3	DU
	0-1	E
	2-3	D
	≥ 4	DU
	0-1	E
	2-3	D
	≥ 4	DU
	0-1	E
	2	S
	3-4	D
	≥ 5	DU
	≤ 2	E
	3-4	D
	≥ 5	DU
	≤ 2	E
	3	S

Number of Evaluable Subjects	Number of DLTs	Decision
	4-5	D
	≥ 6	DU

D = de-escalate to the next lower dose level; DLT = dose-limiting toxicity; DU = the current dose is unacceptably toxic; E = escalate to the next higher dose; S = stay at the current dose

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. Additionally, if dose de-escalation occurs and based on emerging PK, PD and safety data, alternative (intermediate) dose levels may be explored per the recommendations of the DLRM, [redacted]. The recommended phase 2 dose will be estimated using isotonic regression (Ji et al, 2010) and the recommended phase 2 dose will be the dose level with the estimated DLT rate closest to 0.30. In order to consider a certain dose level as the recommended phase 2 dose at least [redacted] DLT evaluable subjects must be enrolled at that dose level.

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 [redacted] evaluable subjects overall).
- One of dose levels is determined to be safe and tolerable (minimum of [redacted] 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.

To minimize the number of subjects treated at potentially toxic dose levels, the first [redacted] subjects in each cohort will be enrolled sequentially with a minimum of [redacted] days between the first dose of these subjects.

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.

Part 2 (Dose Expansion):

Upon completion of Part 1 of the study, enrollment will commence in Part 2 to confirm the safety and tolerability of the selected dose and to further evaluate the efficacy of tarlatamab in combination with AMG 404. Formal safety interim analyses will be

performed for every [redacted] subjects who have had opportunity to have at least [redacted] of follow-up since first dose of tarlatamab. The details are provided in Section 9.4.1.

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

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

4.2 Patient Input into the Study Design

Patient input was not obtained for this study.

4.3 Justification for Dose

4.4 Justification for Investigational Product Dose

4.4.1.1 Tarlatamab

The proposed starting dose and associated dosing schedule for this study is a target dose of [redacted] mg administered with 1-step dosing ([redacted] mg on cycle 1 [redacted] followed by [redacted] mg on cycle 1 [redacted] mg on cycle 1 [redacted] and [redacted] mg [redacted] thereafter). The selection of this starting dose and dosing schedule is based on the safety, tolerability, and preliminary efficacy data from the ongoing FIH study (20160323).

As of 29 September 2021, [redacted] subjects (96.8%) out of [redacted] enrolled in Study 20160323 had received at least 1 dose of tarlatamab given as monotherapy in subjects with relapsed/refractory SCLC (Study 20160323). Subjects were enrolled across doses ranging from [redacted] mg tarlatamab administered IV [redacted] In cohort 8 with a target dose of [redacted] mg with 1-step dosing ([redacted] mg on cycle 1 [redacted] followed by [redacted] mg on cycle 1 [redacted] mg on cycle 1 [redacted] and [redacted] mg [redacted] thereafter), [redacted] subjects were enrolled and received at least 1 dose of tarlatamab. In these [redacted] subjects, all subjects (100%) reported treatment related adverse events of any grade, of which grade 3 or higher treatment related adverse events were reported in [redacted] subjects (70.6%) and serious adverse events were reported in [redacted] subjects (47.1%). Cytokine release syndrome of any grade was reported in [redacted] subjects (52.9%). No treatment-related adverse events leading to discontinuation of tarlatamab were reported in cohort 8. In cohort 10 with a target dose of [redacted] mg with 1-step dosing ([redacted] mg on cycle 1 [redacted] followed by [redacted] mg on cycle 1 [redacted] mg on cycle 1 [redacted] and [redacted] mg [redacted] thereafter), [redacted] subjects were enrolled and received at least 1 dose of tarlatamab. In these [redacted] subjects, [redacted] subjects (100%) reported treatment-related adverse events of any grade, of which grade 3 or higher treatment related adverse events were reported in [redacted] subjects

(46.2%) and serious adverse events were reported in [redacted] subjects (46.2%). Cytokine release syndrome of any grade was reported [redacted] subjects (46.2%), with grade 2 CRS reported in [redacted] subject (8%). No grade 3 or higher CRS was reported in cohort 10. Treatment-related adverse events leading to withdrawal of tarlatamab were reported in [redacted] subjects (15%) in **c**ohort 10.

As a conservative approach, due to the mechanism of action, the starting dose and dosing schedule of tarlatamab in combination with AMG 404 will be 2 dose levels below the highest target dose deemed safe and tolerable for tarlatamab as determined in the ongoing monotherapy FIH study (Study 20160323). Additionally, the potential doses proposed in this study will not exceed a target dose of [redacted] mg, a dose which has been deemed safe and tolerable with a manageable toxicity profile as monotherapy in the ongoing FIH study (Study 20160323).

The selected starting dose and dosing schedule as well as the potential doses that may be used of tarlatamab in combination with AMG 404 is expected to show clinical activity in subjects with SCLC based on the preliminary evidence of efficacy of tarlatamab when administered alone in subjects with SCLC (see Section 2.2.2.3 for additional details).

4.4.1.2 AMG 404

The AMG 404 dose to be used in this study is [redacted] mg IV [redacted] which is the RP2D for monotherapy in subjects with advanced solid tumors. This dose was selected based on the safety, tolerability, PK, and PD of AMG 404 at dose levels of [redacted] mg in subjects with advanced solid tumors in Study 20180143. As of the 14 February 2020 data cut-off date, AMG 404 was safe and well tolerated across the [redacted] and [redacted]-mg dose range with no dose-related increases in frequency or severity of adverse events in subjects and no DLTs. Preliminary PK results were consistent with those for other therapeutic anti-PD-1 monoclonal antibodies. An approximately dose-proportional increase was observed over the dose range of [redacted] mg IV [redacted] preliminary PD results at the [redacted]-mg dose levels were consistent with the expected saturation of receptor occupancy (RO) for these doses given the potent inhibition of PD-1/PD-L1 interactions in vitro with low nanomolar IC_{50} values and preliminary observed AMG 404 exposures in human subjects. Taking into consideration the cumulative preliminary safety, PK, and PD data, the AMG 404 RP2D for monotherapy is [redacted] mg IV [redacted] in subjects with advanced solid tumors.

4.5 End of Study

An individual subject is considered to have completed the study if he/she has completed the last visit shown in the Schedule of Activities. The total study duration for an individual subject is approximately 24 months. The actual duration for individual subjects will vary depending upon tolerability of tarlatamab and AMG 404, evidence of clinical and/or radiological disease progression, and willingness to participate in the 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), including any additional parts in the study (eg, long-term follow-up, [redacted]), as applicable.

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 the following criteria apply:

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

102 Age ≥ 18 years.

103 Subjects with histologically or cytologically confirmed SCLC who progressed or recurred following at least 1 platinum-based regimen

Note: In countries where standard of care first line systemic treatment includes platinum containing chemotherapy in combination with PD-L1 inhibitor, it is required that patients have failed PD-L1 inhibitor therapy as part of their first systemic treatment or have no access to PD-L1 inhibitors.

Note: If patients progress or relapse within 6 months from receiving platinum containing-systemic treatment for limited stage disease, they are eligible for study regardless of receiving PD-L1 containing regimen.

Note: Subjects with a diagnosis of combined small cell carcinoma with predominant small cells (as determined by the local pathologist) may be

considered for inclusion based on investigator discretion and after discussion with the medical monitor.

104 Subjects with disease measurable by modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

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

106 Eastern Cooperative Oncology Group (ECOG) 0 to 1

107 Adequate organ function per local laboratory, defined as follows:

- absolute neutrophil count $\geq$ 1 x 10^9/L
- platelet count $\geq$ 75 x 10^9/L
- hemoglobin $>$ 9 g/dL (90 g/L)
- Estimated glomerular filtration rate based on Modification of Diet in Renal Disease (MDRD) calculation > 45 mL/min/1.73 m^2
- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $<$ 3 x upper limit of normal (ULN) (or $<$ 5 x ULN for subjects with liver involvement).
- total bilirubin (TBL) $<$ 1.5 x ULN (or $<$ 2 x ULN for subjects with liver metastases).
- Prothrombin time (PT)/international normalized ratio (INR) and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) $\leq$ 1.5 x institutional ULN (subjects on stable anticoagulation are permitted)

108 Pulmonary function:

- No clinically significant pleural effusion. Treatment of pleural effusions to meet eligibility is permitted.
- Baseline oxygen saturation > 90% on room air

109 Cardiac function:

- Cardiac ejection fraction ≥ 50%,
- No evidence of clinically significant pericardial effusion as determined by an echocardiogram (ECHO) or multigated acquisition (MUGA).
- No clinically significant electrocardiogram (ECG) findings

110 Minimum life expectancy of 12 weeks.

5.2 Exclusion Criteria

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

Other Medical Conditions

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 cervical carcinoma in situ without evidence of disease.
- Adequately treated breast ductal carcinoma in situ without evidence of disease.
- Prostatic intraepithelial neoplasia without evidence of prostate cancer.
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ.

202 Major surgery within 28 days of first dose of tarlatamab.

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

204 Subject who experienced recurrent grade 2 pneumonitis or severe or life-threatening immune-mediated adverse events or infusion-related reactions including those that lead to permanent discontinuation while on treatment with immuno-oncology agents

205 Subject with evidence of interstitial lung disease or active, non-infectious pneumonitis

206 History of any immune-related colitis. Infectious colitis is allowed if evidence of adequate treatment and clinical recovery exists and at least 3 months interval observed since diagnosis of colitis.

207 History of allergic reactions or acute hypersensitivity reactions to antibody therapies.

208 Positive/non-negative test for Human Immunodeficiency Virus (HIV).

209 Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or peritoneal/pericardial catheter).

- Note: a pleural catheter or dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted

210 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of tarlatamab.

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

Note: Simple **urinary tract infections** 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.

212 Unresolved toxicity 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 from prior anti-tumor therapy that are considered irreversible (defined as having been present and stable for > 21 day) which may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and Amgen

213 History of hypophysitis or pituitary dysfunction

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

- Positive for hepatitis B surface antigen (HBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B).
- Negative HBsAg and positive for hepatitis B core antibody: hepatitis B virus **deoxyribonucleic acid (**DNA**)** by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B.
- Positive Hepatitis C virus antibody (HCVAb): hepatitis C virus **Ribose nucleic acid (**RNA**)** by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C.

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

216 Myocardial infarction and/or symptomatic congestive heart failure (New York Heart Association > class II) unstable angina, or cardiac arrhythmia requiring medication within 12 months of first dose of tarlatamab.

217 Active autoimmune disease that has required systemic treatment (except replacement therapy) within the past 2 years or any other diseases requiring immunosuppressive therapy while on study. Subjects with Type I diabetes, vitiligo, psoriasis, hypo- or hyper-thyroid disease not requiring immunosuppressive treatment are permitted.

Prior/Concomitant Therapy

218 Prior anti-cancer therapy, including anti-PD-1 or anti-PD**-**L1 antibody therapy: at least 28 days must have elapsed between any prior anti- cancer therapy and the first planned dose of tarlatamab

[redacted]

233 Subjects who have received prior tarlatamab therapy or prior DLL3 x CD3 bispecific therapy are not eligible.

219 History of solid organ transplantation.

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

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

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

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

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

225 Female subjects of childbearing potential unwilling to use protocol specified method of contraception (see Section 11.5) during treatment and for an additional:

- [redacted] following the last dose of tarlatamab
- [redacted] following the last dose of AMG 404

226 Female subjects who are breastfeeding or who plan to breastfeed while on study through:

- [redacted] following the last dose of tarlatamab
- [redacted] following the last dose of AMG 404

227 Female subjects planning to become pregnant while on study through

- [redacted] following the last dose of tarlatamab
- [redacted] following the last dose of AMG 404

228 Female subjects of childbearing potential with a positive pregnancy test assessed at Screening by a highly sensitive serum pregnancy test.

229 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional:

- [redacted] following the last dose of tarlatamab
- [redacted] following the last dose of AMG 404

230 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional:

- [redacted] following the last dose of tarlatamab

- [redacted] following the last dose of AMG 404

231 Male subjects unwilling to abstain from donating sperm during treatment and for an additional:

- [redacted] following the last dose of tarlatamab
- [redacted] following the last dose of AMG 404

232 Evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If history of SARS-CoV-2:

- Acute symptoms of COVID-19 within [redacted] prior to first dose of investigational product (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 institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.3).

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

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

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

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

Sites that do not enroll subjects within 6 months of site initiation may be closed.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure

information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. Study Intervention

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

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

A summary of the dosing and administration of each treatment is shown in Table 6-1 below.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 6-1. Investigational Products

Study Treatment Name	Amgen Investigational Product:[a] Tarlatamab	Amgen Investigational Product:[a] AMG 404
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 intravenous (IV) bag with normal saline ([redacted]% sodium chloride) and an IV solution stabilizer. The drug product is formulated with [redacted] mM L-glutamic acid, [redacted]% (w/v) sucrose, [redacted]% (w/v) polysorbate 80, at a final pH of [redacted]	Note: As of Protocol Amendment 3, AMG 404 will not be supplied. AMG 404 is supplied in a 3 mL Type 1 glass tubing vial containing 1 mL deliverable volume of [redacted] mg/mL. The drug product is formulated with [redacted] mM acetate (sodium counterion), [redacted]% (w/v) sucrose, 0.01% (w/v) polysorbate 80, pH [redacted] and will be prepared for IV administration by dilution.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	The starting dose and dosing schedule of tarlatamab will be [redacted] mg as the target dose with 1-step dosing. Tarlatamab will be administered [redacted] after the target dose is reached. If the combination of tarlatamab and AMG 404 is not tolerated (based on target DLT rate > 30%), tarlatamab dose level will be further dose reduced or the day of administration of AMG 404 in combination with tarlatamab will be adjusted.	[redacted] mg [redacted]
Route of Administration	IV	IV
Accountability	The total volume of preparation, dose, start date/time, stop date/time, and lot number are to be recorded on each subject's CRF(s).	The total volume of preparation, dose, start date/time, stop date/time, and lot number are to be recorded on each subject's CRF(s).
Dosing Instructions	Tarlatamab will be administered as a short-term IV infusion for 60 minutes (± 10 minutes) followed by a flush once [redacted] (except in cycle 1 where 1-step-dosing will be implemented).	[redacted] AMG 404 will be delivered using infusion pumps approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment. AMG 404 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines. The drug will be administered as a short-term IV infusion at a constant flow rate over 30 minutes (± 5 minutes) every [redacted] (± 3 days).

CRF = case report form; DLT = dose limiting toxicity; IV = intravenous; [redacted]

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

6.1.2 Non-investigational Products

No non-investigational products will be administered in this study.

6.1.3 Medical Devices

No medical devices will be used in this study.

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

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

6.1.4 Other Protocol-required Therapies

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

Dexamethasone [redacted] mg IV (or equivalent dose of other corticosteroids) will be administered within 1 hour prior to all cycle 1 doses of tarlatamab including all step doses. Dexamethasone dose and schedule may be changed based on emerging safety data.

Additionally, prophylaxis with IV hydration (1L normal saline over 4 to 5 hours) will be administered:

- immediately following all tarlatamab doses in cycle 1

Additionally, based upon emerging PK, PD, and safety data in the current study as well as the ongoing FIH study (20160323), the premedication regimen may be modified (including with additional prophylactic therapies) as per the recommendations of the DLRT.

To mitigate the risk of CRS, sites are required to have tocilizumab or siltuximab (if tocilizumab is not available) on site.

6.1.5 Other Intervention Procedures

There are no other treatment procedures in this study.

6.1.6 Product Complaints

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

This includes any investigational/non-investigational product(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen (ie, tarlatamab and AMG 404) for which Amgen wants to collect complaints.

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

6.1.7 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 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 [redacted] before the subsequent dose of tarlatamab.

- 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 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, bacille Calmette-Guerin (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 [redacted] 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-Exploration

The dose-exploration part of the study will estimate the recommended phase 2 dose of tarlatamab in combination with AMG 404 using an mTPI2 design. The starting dose and dosing schedule of tarlatamab will be [redacted] mg as the target dose with 1-step dosing. The planned dose levels are shown in Table 4-1.

6.2.1.2 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 recommended phase 2 dose. 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.

Dose Cohort Stopping Rules

For details on dose escalation and stopping rules, refer to Section 4.1.

6.2.1.3 Step Dosing

Due to its known mechanism of action, subjects are at an increased risk for CRS during initiation of tarlatamab treatment. To mitigate this risk, tarlatamab will be administered with the following dosing schedule:

- One-step dosing involving a first step dose on [redacted] mg), followed by a step dose on [redacted] (equal to the target dose) and the target dose on [redacted] then [redacted]

6.2.1.4 Dose-limiting Toxicities

Dose-limiting toxicities are defined as any adverse event with an onset within first [redacted] following first dose of tarlatamab with any of the following criteria unless clearly related to causes other than tarlatamab:

- All grade 3 adverse events except

  - Fatigue lasting less than 7 days
  - 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 6.8.5)
  - Endocrinopathies, if manageable with replacement therapy
  - Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
  - Grade 3 amylase or lipase values that are not associated with symptoms or clinical manifestations of pancreatitis
  - Grade 3 hematologic lab abnormalities that are not considered clinically relevant
  - Grade 3 electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
- Grade 4 adverse event regardless of duration, except:
  - 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 6.8.5)
  - Grade 4 electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
  - Grade 4 amylase or lipase values that are not associated with symptoms or clinical manifestations of pancreatitis
  - Grade 4 hematologic lab abnormalities that are considered not clinically relevant
- Grade 5 adverse events
- Recurrent grade 2 or higher pneumonitis
- Without exception, any other toxicity requiring permanent discontinuation of AMG 404 per Table 6-2.

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

- Lymphopenia
- Fever
- Tumor lysis syndrome 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 CRFs.

6.2.2.1.1 Dosage Adjustment

Subjects should continue on the same target dose of tarlatamab (not including the initial first step dose and step doses) throughout the study with the exception of subjects who experienced a DLT or other intolerable tarlatamab-related adverse events but show evidence of clinical benefit. These subjects will have the 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 (Section 4.1). The study drug can be resumed once the adverse events recover to grade ≤ 1, and the reintroduction of tarlatamab is deemed safe and tolerable by the investigator, Medical Monitor, and GSO. The subject must be informed of the risk of continuing on therapy. Each subject is allowed one dose reduction. For adverse events related to CRS, neurological events, and pituitary dysfunction, please see Sections 6.8.1, 6.8.3, and 6.8.4, respectively, for guidelines for dose adjustments.

If restarting tarlatamab due to adverse events, dose reductions would occur with tarlatamab (as described in Section 6.8). The study drug can be resumed once the adverse events recover to grade 0 to 1 and the reintroduction of tarlatamab is deemed safe by the investigator, Medical Monitor, and GSO.

6.2.2.1.2 Dose Delays

During the first [redacted] 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 [redacted] 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. 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 3 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. 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, 6.8.3, and 6.8.4 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 6.8.4)
- Criteria for conditional withholding of tarlatamab due to potential hepatotoxicity (Section 11.7)

Tarlatamab dosing can be resumed if the toxicities resolve to grade ≤ 1 or return to subjects' baseline values within 3 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:

- Criteria for permanent withholding of tarlatamab due to potential hepatotoxicity (Section 11.7)
- Any grade ≥ 4 adverse events except those not considered DLT as described in Section 6.2.1.4
- Grade 3 adverse event(s) that do not recover to grade ≤ 1 within 3 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 3 weeks)

For adverse events related to CRS, neurological events and pituitary dysfunction, please see Sections 6.8.1, 6.8.3, and 6.8.4 respectively for guidelines for dose adjustment.

6.2.2.1.4 Criteria to Pause Enrollment

At any point during the study, enrollment will be paused at the occurrence of 2 or more of the same grade 4 or one or more grade 5 investigational product-related adverse events. The 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 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 1 more grade 5 investigational product-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.)

6.2.2.2 Amgen Investigational Product: AMG 404

[redacted]

6.2.2.2.1 Immune-related Adverse Reactions

Adverse events following the administration of AMG 404 may represent an immunologic etiology. Based on clinical experience with other anti-PD-L1 therapies, these immune-related toxicities may occur shortly after the first dose to several months after the last dose of treatment and may affect more than 1 body system simultaneously. Early recognition and management are critical to reduce complications.

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

Based on the type and severity of the immune-related adverse event, withholding or permanent discontinuation of AMG 404 may be required, in addition to treatment with corticosteroids and/or other therapies. Dose modification and toxicity management guidelines for immune-related adverse reactions are provided in Table 6-2.

6.2.2.2.2 Infusion-related Reactions

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

For mild or moderate infusion-related reactions, interrupt or slow the rate of infusion. For severe or life-threatening infusion-related reactions, permanently discontinue AMG 404. Treatment guidelines for infusion reactions associated with the administration of AMG 404 are provided in Table 6-3.

Table 6-2. AMG 404 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events

Immune-Related Adverse Reactions	Severity or Specific Conditions	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Pneumonitis	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Withhold	Administer corticosteroids at an initial dose of 1 to [redacted] mg/kg/d prednisone (or equivalent) followed by taper. Consider additional immunosuppressive agent (eg, infliximab, mycophenolate, cyclophosphamide) if refractory to corticosteroids.	Monitor subjects for signs and symptoms of pneumonitis. Evaluate subjects with suspected pneumonitis with radiographic imaging. Add prophylactic antibiotics for opportunistic infections.
	Recurrent grade 2	Permanently discontinue		
	Grade 3 (severe symptoms, limiting self-care ADL, oxygen indicated)			
	Grade 4 (life-threatening respiratory compromise, urgent intervention indicated [eg, tracheotomy or intubation])			
Colitis/Diarrhea	Grade 2 (increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline)	Withhold	Administer corticosteroids at an initial dose of 1 to [redacted] mg/kg/d prednisone (or equivalent) followed by taper. Consider infliximab if symptoms refractory to corticosteroids within 2 to 3 days.	Monitor subjects for signs and symptoms of enterocolitis (eg, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (eg, peritoneal signs and ileus). For subjects with grade $\geq$ 2 diarrhea suspecting colitis, consider GI consultation and endoscopy to rule out colitis.
	Grade 3 (increase of 7 or more stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL)			
	Grade 4 (life-threatening consequences; urgent intervention indicated)	Permanently discontinue		

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Table 6-2. AMG 404 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events

Immune-Related Adverse Reactions	Severity or Specific Conditions	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Hepatotoxicity	When applicable, refer to Section 11.7 for managing AST and/or ALT and/or total bilirubin elevations, when other liver parameters remain within normal limits (eg, INR).			
Immune-mediated hepatitis[a] (Adapted from NCCN Guidelines)	Grade 1 (AST or ALT > ULN but < 3 x ULN) without elevated total bilirubin	Continue	Consider holding for concerning lab value trend.	Monitor with liver function tests more frequently until returned to baseline or stable. Additional management per institutional and professional society guidelines.
	Grade 2 (AST or ALT 3 to 5 x ULN) without elevated total bilirubin	Withhold	Consider corticosteroids at an initial dose of [redacted] mg/kg/d prednisone (or equivalent) followed by taper.	
	Grade 3 (AST or ALT 5 to 20 x ULN) without elevated total bilirubin (Without a clear alternative etiology. If a clear alternative etiology, then withhold, do not discontinue AMG 404.)	Permanently discontinue	Administer corticosteroids at an initial dose of [redacted] mg/kg/d prednisone (or equivalent) followed by taper. Consider mycophenolate mofetil if refractory to corticosteroids or no improvement after 3 days.	
	Grade 4 (AST or ALT > 20 x ULN) without elevated total bilirubin (Without a clear alternative etiology. If a clear alternative etiology, then withhold, do not discontinue AMG 404.)		Administer corticosteroids at an initial dose of [redacted] mg/kg/d prednisone (or equivalent) followed by taper. Consider mycophenolate mofetil if refractory to corticosteroids or no improvement after 3 days.	
	Grade > 1 (AST or ALT > 3 x ULN) with total bilirubin > 1.5 x ULN [Without a clear alternative etiology. If a clear alternative etiology, then withhold, do not discontinue. Consider holding for concerning lab value trend.]		Administer corticosteroids at an initial dose of [redacted] mg/kg/d prednisone (or equivalent) followed by taper. Consider mycophenolate mofetil if refractory to corticosteroids or no improvement after 3 days.	

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Table 6-2. AMG 404 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events

Immune-Related Adverse Reactions	Severity or Specific Conditions	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Hypophysitis (Event reported as Endocrine disorders, Other, Hypophysitis)	Grade 3 or 4 (Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL, or; Life-threatening consequences; urgent intervention indicated)	Withhold	Administer corticosteroids at an initial dose of [redacted] mg/kg/d prednisone (or equivalent) followed by taper. In addition, initiate hormonal replacement therapy as clinically indicated.	Monitor for signs and symptoms of hypophysitis. Consider endocrine consultation.
Adrenal Insufficiency	Grade 3 or 4 (severe symptoms, hospitalization indicated or life-threatening consequences, urgent intervention indicated)	Withhold	Initiate IV stress-dose corticosteroids on presentation (hydrocortisone [redacted] mg or dexamethasone [redacted] mg [if the diagnosis is not clear and ACTH stimulation testing will be needed]). Taper stress-dose corticosteroids down to maintenance doses (prednisone 5 to [redacted] mg daily) over 1 to 2 weeks after discharge.	Monitor for signs and symptoms of adrenal insufficiency. Consider endocrine consultation.
Hypothyroidism	Grade 3 or 4 (severe symptoms, limiting self-care ADL; hospitalization indicated or life-threatening consequences, urgent intervention indicated)	Withhold	Initiate thyroid hormone supplementation.	Monitor subjects for signs and symptoms of hypothyroidism. Consider endocrine consultation.
Hyperthyroidism	Grade 3 or 4 (severe symptoms, limiting self-care ADL; hospitalization indicated or life-threatening consequences, urgent intervention indicated)	Withhold	Initiate β-Blocker (eg, atenolol, propranolol) for symptomatic relief. For severe symptoms or concern for thyroid storm, initiate prednisone [redacted] mg/kg/d (or equivalent) tapered over 1 to 2 weeks. Consider use of SSKI or thionamide (methimazole or PTU).	Monitor subjects for signs and symptoms of hyperthyroidism. Consider endocrine consultation.

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Table 6-2. AMG 404 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events

Immune-Related Adverse Reactions	Severity or Specific Conditions	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Diabetes Mellitus	Grade 3 hyperglycemia (> [redacted] mg/d [> [redacted] mmol/L]; hospitalization indicated)	Withhold	Initiate insulin therapy.	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes. Consider endocrine consultation.
	Grade 4 hyperglycemia (> [redacted] mg/dL [> [redacted] mmol/L]; life-threatening consequences)			
Nephritis and Renal Dysfunction	Grade 2 (serum creatinine >1.5 to 3.0 x baseline; >1.5 to 3.0 x ULN)	Withhold	Administer corticosteroids at an initial dose of [redacted] to [redacted] mg/kg/d prednisone (or equivalent) followed by taper. If worsening or no improvement occurs, increase dose of corticosteroids to [redacted] to [redacted] mg/kg/d prednisone (or equivalent).	Monitor changes in renal function. Evaluate for other causes of renal dysfunction (eg, recent IV contrast, medications, fluid status, etc,)
	Grade 3 (serum creatinine > 3.0 x baseline; > 3.0 to 6.0 x ULN)	Permanently discontinue	Administer corticosteroids at an initial dose of [redacted] mg/kg/d prednisone (or equivalent) followed by taper.	
	Grade 4 (serum creatinine > 6 x ULN)			

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Table 6-2. AMG 404 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events

Immune-Related Adverse Reactions	Severity or Specific Conditions	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold	Administer corticosteroids at an initial dose of [redacted] mg/kg/d prednisone (or equivalent) followed by taper. Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids as indicated.	Monitor subjects for suspected severe skin reactions and exclude other causes (eg, infection, an effect of another drug, a skin condition linked to another systemic disease, etc,). For signs or symptoms of SJS or TEN, withhold study drug and refer the patient for specialized care for assessment and treatment.
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue		
Encephalopathy	Grade 2 (moderate symptoms, limited instrumental ADL)	Withhold	Administer corticosteroids at an initial dose of [redacted] mg/kg/d prednisone (or equivalent) followed by taper. Consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results obtained and negative for aseptic meningitis.	Monitor subjects for neurologic symptoms and exclude other etiologies (eg, infectious). Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.
	Grade 3 or 4 (Severe symptoms; limiting self-care ADL; or life-threatening consequences; urgent intervention indicated)	Permanently discontinue (If event not attributable to tarlatamab)		

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Table 6-2. AMG 404 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events

Immune-Related Adverse Reactions	Severity or Specific Conditions	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Myocarditis	Grade 1 (asymptomatic with laboratory [eg, BNP] or cardiac imaging abnormalities)	Withhold	Administer corticosteroids at an initial dose of [redacted] mg/kg/d prednisone (or equivalent) followed by taper.	Monitor patients with cardiovascular symptoms. Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 2 (symptoms with mild to moderate activity or exertion)	Permanently discontinue		
	Grade 3 (severe with symptoms at rest or with minimal activity or exertion; intervention indicated)			
	Grade 4 (life-threatening consequences; urgent intervention indicated [eg, continuous IV therapy or mechanical hemodynamic support])	Permanently discontinue		
All Other Immune-Related Adverse Reactions	Grade 3 adverse reaction involving a major organ	Withhold	Based on type and severity of adverse reaction, administer corticosteroids. Refer to ASCO Clinical Practice Guidelines for additional recommendations.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Life-threatening or grade 4 adverse reaction involving a major organ	Permanently discontinue		
Recurrent or Persistent Immune-Related Adverse Reactions	Recurrence of same grade 3 or grade 4 adverse reaction	Permanently discontinue	Based on type and severity of adverse reaction, administer corticosteroids. Additional immunosuppressive treatment may be required.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Requirement for ≥ [redacted] mg/day prednisone (or equivalent) for more than 12 weeks			
	Persistent grade 2 or 3 adverse reactions lasting 12 weeks or longer after last dose (ie, does not resolve to grade 0 or 1 within 12 weeks)			

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NOTE: Recommendations adapted from the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines for the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy (Brahmer et al, 2018).

General considerations:

- Corticosteroid taper should be initiated upon improvement of signs/symptoms and/or laboratory values to grade 1 or less. Continue corticosteroid taper over the course of at least 4 to 6 weeks.
- If AMG 404 has been withheld, treatment with AMG 404 may be resumed after adverse event (or associated signs/symptoms/laboratory parameters) has been reduced to grade 1 or less and corticosteroid has been tapered to prednisone < [redacted] mg (or equivalent).
- For severe and life-threatening immune-related adverse reactions, IV corticosteroids should be initiated first followed by oral corticosteroids. Other immunosuppressive treatment should be initiated if the event cannot be controlled by corticosteroids.

ACTH = adrenocorticotropic hormone; ADL = activities of daily living; ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; BNP = B-natriuretic peptide; CSF = cerebral spinal fluid; ECG = electrocardiogram; GI = gastrointestinal; INR = international normalized ratio; IV = intravenous; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PTU = propylthiouracil; SJS = Stevens-Johnson syndrome; SSKI = saturated solution of potassium iodide; TEN = toxic epidermal necrolysis; ULN = upper limit of normal

[a] Immune-mediated hepatitis guidance adapted from the NCCN Version 1.2020, Management of Immune Checkpoint Inhibitor-Related Toxicities

Table 6-3. Management of Infusion-Related Reactions With AMG 404

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

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Table 6-3. Management of Infusion-Related Reactions With AMG 404

Severity	AMG 404 Dose Modification	Management	Premedication at Subsequent Dosing
Grade 3 (prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae) *OR* Grade 4 (life-threatening consequences; urgent intervention indicated)	Permanently discontinue study drug.	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Hospitalization may be indicated. • Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids, and epinephrine. In cases of anaphylaxis, epinephrine should be used immediately.	No subsequent dosing

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IV = intravenous; NSAIDs = non-steroidal anti-inflammatory drugs

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 drug accountability for the investigational product will be provided to the site.

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 and AMG 404.

6.4.2 Blinding

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

6.5 Treatment Compliance

When subjects are dosed at the site, they will receive tarlatamab and AMG 404, or tarlatamab monotherapy [redacted], directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

6.6 Treatment of Overdose

The effects of overdose of these products 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 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” 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 SCLC, collect therapy name, indication, dose, unit, frequency, route, start and stop dates.

All prior cancer treatment therapies will be collected.

For all prior therapies taken for SCLC (eg, chemotherapy, immunotherapy, biological therapy or targeted 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
- reason for discontinuation (disease progression, clinical progression, toxicity, subject’s decision)

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 6.1.7.

All prescription and nonprescription concomitant therapies are to be collected from informed consent through the end of safety follow-up (SFU) period. Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date and record in the electronic case report form (eCRF).

6.8 Support Care and Potential Risk Management Guidelines for Tarlatamab

6.8.1 Cytokine Release Syndrome

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

- Constitutional : fever ± rigors, malaise, fatigue, anorexia, myalgias, 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
- Skin: rash
- Gastrointestinal: nausea, vomiting, diarrhea
- 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

Cytokine release syndrome 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. Cytokine release syndrome may be life-threatening or fatal. Infusion reactions may be clinically indistinguishable from manifestations of CRS. Subjects will be hospitalized for intensive monitoring in cycle 1 and cycle 2 as described in Section 8.1.2. Throughout the infusion with tarlatamab and after the end of infusion (EOI) (as described in Section 8.1.2), 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 6-4. For subjects with suspected CRS, samples may be collected for analysis after discussion with the Medical Monitor.

Table 6-4. 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 medical monitor). Permanently discontinue tarlatamab if there is no improvement to CRS ≤ grade 1 within 7 days.

Table 6-4. Grading and Management of Cytokine Release Syndrome

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 [redacted] mg ([redacted] mg/day). The dose should then be reduced step-wise. Investigators should consider use of tocilizumab[c] [redacted] mg/kg over 1 hour (not to exceed [redacted] mg). Repeat tocilizumab[c] every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Maximum of 3 doses in a [redacted] period. Maximum total of 4 doses. 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 or reduce to next lower dose of tarlatamab if CRS grade 3 occurs at the initial first step dose.
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 [redacted] mg ([redacted] mg/day). Further steroid use should be discussed with the Amgen medical monitor. Investigators should consider use of tocilizumab[c] [redacted] mg/kg IV over 1 hour (not to exceed [redacted] mg). Repeat tocilizumab[c] every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Maximum of 3 doses in a [redacted] hour period. Maximum total of 4 doses. Investigators may also consider additional therapy, based on clinical judgment.	If CRS occurs during tarlatamab treatment, immediately stop the infusion. Permanently discontinue tarlatamab therapy.

CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; N/A = not applicable

[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 Table 6-4. The recommended dose of siltuximab is [redacted] 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.

Re-start of treatment after CRS:

After a grade 3 CRS event, the next infusion may be administered if all 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 Immune-effector Cell-associated Neurologic Syndrome

For this trial, ICANS will be using the criteria referenced in the publication by Lee et al, 2019. While the grading system has been developed in large part from CAR-T therapies, symptoms of ICANS may be shared among immune effector cell-associated therapies such as BiTE molecules. Although there may be a wide range of symptoms associated with ICANS, subjects may have a stereotypic course of a specific set of symptoms. The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy.

Immune effector cell-associated neurologic syndrome grade is determined by the most severe event (eg, depressed level of consciousness, seizure, motor findings, raised intracranial pressure [ICP]/cerebral edema) not attributable to any other cause. Refer to the immune effector cell-associated encephalopathy (ICE) score below for grading of ICANS.

Immune Effector Cell-associated Encephalopathy (ICE) Assessment Tool

The ICE tool was designed to provide objectivity for the grading of multiple overlapping encephalopathy terms. The tool includes an element for assessing the receptive aphasia seen in these subjects. The total score that after assessing the following questions will be used as an input in the determination of the ICANS grade.

- **Orientation: Orientation to year, month, city, hospital: 4 points**
- **Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points**
- **Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point**

- **Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point**
- **Attention: ability to count backwards from 100 by 10: 1 point**

ICE Scoring

- **7-9, grade 1**
- **3-6, grade 2**
- **0-2, grade 3**
- **0 due to subject unarousable and unable to perform ICE**
- **Assessment, grade 4**

Table 6-5 ASBMT Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults

Neurotoxicity Domain[a]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[b]	7-9	3-6	0-2	0 (subject is unarousable and unable to perform ICE)
Depression level of consciousness[c]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[d]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[e]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ASBMT = American Society for Blood and Marrow Transplantation; CTCAE = Common Terminology Criteria for Adverse Events; EEG = electroencephalogram; ICANS = immune effector cell-associated neurologic syndrome; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; N/A = not applicable.

[a] Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to immune effector-cell engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted.

[b] A subject with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a subject with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[c] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[d] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[e] Intracranial haemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Source: Lee et al, 2019

Refer to the regional prescribing information or institutional guidelines (if not addressed in prescribing information) for additional information regarding standard of care therapy.

6.8.3 Neurologic Events

Please see **Table 6-6** 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 6-6. Management of Adverse Events Related to Neurologic Events

Toxicity	Grade[a]	Instructions for Treatment Interruption and Restart
Neurologic Events	3[b]	• 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 1 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

[a] Per Common Terminology Criteria for Adverse Events (CTCAE) Guidelines Version 4.0
[b] For adverse events grade ≤ 2, please follow institutional guidelines for management.

6.8.4 Pituitary Dysfunction

Based on the expression of DLL3 in the pituitary and observations in the cynomolgus monkey toxicology study, 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 **Table 6-7**. Adrenocorticotropic hormone (ACTH), cortisol, TSH, free thyroxine (FT4) will be evaluated at screening and monitored throughout the study. Prolactin and follicle stimulating hormone (FSH)/luteinizing hormone (LH), testosterone (in males) and estradiol (in females) will also be evaluated at screening, end of therapy and as clinically indicated. After a confirmed diagnosis, tarlatamab will be withheld, and corticosteroids and hormone replacement administered if clinically indicated. Please see Section 6.2.2.1.3 for guidelines for restarting tarlatamab. This management recommendation may be revised based on emerging clinical data.

Table 6-7 Monitoring and Management of Pituitary Gland Dysfunction (González-Rodríguez and Rodríguez-Abreu, 2016; Brahmer et al, 2018)

- Monitor for signs and symptoms of pituitary gland dysfunction, TSH, FT4, cortisol, and ACTH throughout study (prolactin, FSH, LH, testosterone [in males] and estradiol [in females] will be evaluated only at screening, EOT, and as clinically indicated)
  - Abnormal hormone monitoring result or clinical suspicion of pituitary gland dysfunction (headache, fatigue, asthenia, impaired vision, vomiting, hypotension, amenorrhea, impotence)
  - Diagnostic tests: consider brain MRI (if clinically indicated) with or without contrast with pituitary/sellar cuts in subjects with multiple endocrine abnormalities and/or with new headache or vision changes. Evaluate ACTH, AM Cortisol, TSH, FT4, electrolytes and consider evaluating LH, FSH, and testosterone levels in males or estrogen females.
- Obtain endocrinology consultation for hypophysitis or if clinically indicated
- Once pituitary gland dysfunction is confirmed, hold further treatment with tarlatamab pending completion of evaluation. Manage pituitary dysfunction according to NCCN or ASCO guidelines for Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy (NCCN Guidelines, 2021; Brahmer et al, 2018).
- Once stabilized on any replacement hormones and taking [redacted] mg or less of prednisone or equivalent may consider restarting tarlatamab. If subject experienced grade 3 or higher pituitary dysfunction, must discuss with medical monitor prior to restarting treatment.
- Continue endocrinological surveillance

ACTH = adrenocorticotropic hormone; **ASCO = American Society of Clinical Oncology;** EOT = end of treatment; FSH = follicle stimulating hormone; FT4 = free thyroxine; LH = luteinizing hormone; MRI = magnetic resonance imaging; **NCCN = National Comprehensive Cancer Network;** TSH = thyroid stimulating hormone

6.8.5 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 [WBC] 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 6-8**.

Table 6-8. Tarlatamab Dose Modification Guidelines for Neutropenia

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 2 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 that lasts > 7 days

G-CSF = granulocyte colony-stimulating factor

6.8.6 Tumor Lysis Syndrome

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. Tumor lysis syndrome 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 bulky, SCLC 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). Intravenous hydration and careful monitoring of fluid status is recommended. Allopurinol or rasburicase can be considered for both prophylaxis and/or treatment of hyperuricemia.

6.8.7 Vaccines

Every effort should be made to fully vaccinate patients prior to [redacted] days from first dose of tarlatamab. The use of vaccines except live and live-attenuated vaccines will be allowed during therapy per regional and institutional standard of care. However, SARS-CoV-2 vaccinations should be avoided during screening (within a minimum of [redacted] days from first dose of tarlatamab) and should be also avoided in the first treatment cycle for better assessment of safety parameters. Throughout the trial, SARS-CoV-2 vaccination should be avoided within [redacted] days after the administration of tarlatamab. In the event where a patient requires steroids for treatment of adverse events, vaccination should be avoided while on steroids.

6.8.8 Management of SARS-CoV-2 Infection and COVID-19 Disease

Management of SARS-CoV-2 infection and COVID-19 should be performed according to the guidelines provided in **Table 6-9** (exceptions may be permitted with medical monitor approval).

Table 6-9. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of SARS-CoV-2 Infection and COVID-19 Disease

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
SARS-CoV-2 infection and COVID-19 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 and 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, ECG, ECHO, and cardiology assessment prior to re-start of **investigational product**. 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 investigational product only after discussion with patient and reassessment of individual risk/benefit and perform CT of chest imaging and ECG required prior to re-start of investigational product. Consider ECHO and cardiology assessment • Consider hospitalization for re-start of investigational product 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 • Premedication and assessments: follow guidance in SOA tables	Immediately stop the infusion (if applicable) and permanently discontinue investigational product 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 no longer favorable

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Footnotes defined on last page of this table.

Table 6-9. Infusion Interruptions/Delays/Withholding/Permanent Discontinuation and Management of SARS-CoV-2 Infection and COVID-19 Disease

Grade	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
SARS-CoV-2 infection and COVID-19 disease				
Symptomatic	Interruption required until at least 10 days since complete resolution of acute symptoms	Follow local guidelines and standard of care for COVID-19 treatment and isolation Contact Amgen Medical Monitor within 1 business day to ensure appropriate documentation and management of study activities	• Re-start possible upon agreement between investigator and Amgen medical monitor provided: ○ There are no new findings on physical exam and chest imaging, related to SARS-CoV-2 ○ Subject tests negative for SARS-CoV-2 by RT-PCR ○ Consider CT of the chest imaging and ECG, ECHO and cardiology assessment prior to re-start of **investigational product**. OR ○ If subject continues to test positive for SARS-CoV-2 more than 10 days after initial positive test, resume investigational product only after discussion with patient and reassessment of individual risk/benefit and perform CT of chest imaging and ECG required prior to re-start of investigational product. Consider ECHO and cardiology assessment • Consider hospitalization for re-start of investigational product 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 • Premedication and assessments: follow guidance in SOA tables	Immediately stop the infusion (if applicable) and permanently discontinue investigational product 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 no longer favorable

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COVID-19 = coronavirus disease 2019; CRS = cytokine release syndrome; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; RT PCR = real time polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOA = Schedule of Activities

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

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

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 1.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies and/or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 1.3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product**,** and/or other protocol-required therapies and/or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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

- Decision by sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Non-compliance

- Confirmed disease progression as defined by modified RECIST 1.1 criteria (Section 11.9) or disease progression accompanied by worsening of symptoms or deterioration of the subject's general condition

  *Note: Subjects with confirmed disease progression per modified RECIST 1.1 criteria who have clinical benefit in the investigator's judgment may be allowed to continue treatment after approval by the Medical Monitor as per Section 7.2
- Requirement for alternative therapy
- Protocol-specified criteria:

  Subjects who require more than 1 dose reduction

7.2 Continuation on Study Treatment After Radiologic Disease Progression

This section details the conditions necessary to allow continued treatment with tarlatamab after radiologic disease progression in subjects that continue to have clinical benefits in the investigator's judgement, provided all of the following criteria are met at each occurrence:

- Absence of threat to vital organs or critical anatomical sites (eg, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention with persistent immediate threat to vital organs after intervention. The presence of brain metastases may be allowed, provided the lesions are amenable to radiation therapy or dexamethasone (or corticosteroid equivalent) and the subject is clinically stable as per investigator's judgment.
- No other treatment discontinuation criteria are met.
- No significant, unacceptable, or irreversible toxicities related to any dose of the study treatment or treatment related adverse events of CTCAE grade 4 at the current dose at the time of progression.
- The subject is willing to undergo biopsy of one of the new or progressing lesions. If tumor biopsy is not clinically feasible or advisable, the subject may continue only upon agreement with the investigator and the Amgen Medical Monitor.
- Approval for continuation from the Amgen Medical Monitor.
- Palliative radiation for new, progressive, or symptomatic lesions is permitted as per Section 6.1.7. Tarlatamab must be held during treatment and radiation and must be completed at least [redacted] days before the subsequent dose of tarlatamab.
- All protocol-mandated procedures must be performed as noted in the Schedule of Activities (Section 1.3) (imaging, labs, and clinic visits may be obtained earlier per clinical judgment and if clinically indicated).

7.3 Subject Discontinuation/Withdrawal from the Study

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

subject appropriate procedures for withdrawal from the study and must document the subject's decision to withdraw in the subject's medical records.

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

7.3.1 Reasons for Removal from Study

Reasons for removal of a subject from the study are:

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

7.4 Lost to Follow-up

A subject will be considered lost to follow-up if they repeatedly fail 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 should 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).

If an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

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

8.1 General Study Periods

8.1.1 Screening, Enrollment and/or Randomization

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

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 [redacted] screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Treatment begins on cycle 1 [redacted] when the first IV infusion of investigational product is administered to a subject. The following procedures will be completed during the treatment period at the times designated in the Schedule of Activities (Section 1.3). The results of the cycle 1 [redacted] 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 [redacted] dosing where laboratory assessments that were done within 48 hours prior to infusion do not need to be repeated). 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 (Section 1.3). 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 end of treatment (EOT) visit will occur at the end of the last treatment cycle. For subjects who prematurely discontinue investigational product treatment, the EOT visit should occur as soon as possible (within [redacted]) after the last dose of investigational product was administered.

8.1.3 Safety Follow-up

The procedures to be completed during SFU are indicated in the Schedule of Activities (Section 1.3). Upon permanent discontinuation from the study treatment for any reason, an SFU visit will be performed approximately [redacted] after the last dose (tarlatamab or AMG 404) or prior to initiation of other therapy, whichever occurs first. The second safety follow-up visit will be performed approximately [redacted] after the end of the last dose of AMG 404 or prior to initiation of other therapy, whichever occurs first.

Subjects who discontinue AMG 404 but remain on treatment with AMG 757 will continue to have safety event collection at regularly scheduled study visits. The second safety follow-up visit need only occur if [redacted] has not elapsed from the end of AMG 404 treatment at the time of end of study treatment.

8.1.4 Long-term Follow-up

Long term follow-up will be conducted every 3 months (± 2 weeks) up to 1 year 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 (computed tomography [CT]/MRI) of the chest, abdomen, pelvis, and all other known sites of disease every 3 months until documentation of confirmed disease progression per modified RECIST 1.1, clinical progression, start of new anticancer therapy, or up to 12 months after the first dose of tarlatamab, whichever occurs first.

8.1.5 End of Study

The End of Study visit is defined as the date of the final study visit (eg, final long-term follow-up visit) when assessments and/or procedures are performed.

8.2 General Assessments

8.2.1 Informed Consent

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

8.2.2 Demographics

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

8.2.3 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 CRF. In addition to the medical history above, SCLC history must date

back to the original diagnosis. 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 the CTCAE version 4.0 (See Section 11.4) unless specified otherwise.

All prior cancer therapies will be collected.

8.2.4 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).

8.2.5 Physical Measurements

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

8.2.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of tobacco.

8.2.7 Performance Status

The subject's performance status will be assessed using the ECOG performance scale (see Section 11.8).

8.3 Efficacy Assessments

8.3.1 Radiologic Imaging Assessment

The extent of disease will be evaluated by contrast-enhanced MRI/computed tomography (CT) according to modified RECIST 1.1 (Section 11.9).

[redacted]

Due to the mechanism of action of immune-enhancing therapies, subjects may experience delayed response or enhanced T-cell expansion and infiltration into tumors, leading to an apparent enlargement of existing lesions or the appearance of new lesions prior to maximal clinical benefit being observed.

[redacted]. All brain scans on protocol are required to be MRI unless MRI is contraindicated, and then CT with contrast is acceptable.

[redacted].

Determination of disease response for clinical management of subjects will be assessed at the clinical sites per modified RECIST 1.1. Scans may be submitted to a central imaging core laboratory for archival, response assessment including modified RECIST 1.1, and/or [redacted] eg, volumetric and viable tumor measurements. Detailed information regarding submission of images to the central imaging core laboratory is found in the Imaging Procedural Manual.

8.4 Safety Assessments

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

8.4.1 Vital Signs and Pulse Oximetry

Vitals signs (blood pressure [BP], RR, HR, and temperature) and pulse oximetry will be recorded by the investigator or designee at time points specified in the Schedule of Assessments (Section 1.3).

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

In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute after the initial reading, with the **2** readings averaged to obtain a final blood pressure measurement. The average value should be recorded in the eCRF.

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

Vital signs will be taken pre-AMG 404 infusion and at AMG 404 EOI. After each tarlatamab infusion for the first 2 cycles (during the hospitalization period), vital signs will be assessed accordingly during the following timepoints:

8.4.2 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.

8.4.3 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.

8.4.4 Mini-Mental Status Examination

The Mini Mental Status Examination (MMSE) Version 2 will be performed as outlined in the Schedule of Activities (Section 1.3). The MMSE is a 30-point healthcare professional (including study coordinators) administered questionnaire to assess potential subjects for cognitive impairment. The assessment covers 8 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.

8.4.5 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

Principal Investigator 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. See Section 1.3 for timing of ECG assessments.

8.4.6 Clinical Laboratory Assessments

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

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

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

8.4.7 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.

8.4.8 Other Safety

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

Echocardiogram or MUGA will be performed to assess cardiac ejection fraction and will occur at time points specified in the Schedule of Activities (Section 1.3).

Echocardiography/MUGA should include an evaluation from left ventricular ejection fraction (LVEF). Additional ECHO/MUGA assessments may be performed as clinically indicated. For subjects developing COVID-19 during screening period and following screening imaging assessments, consider repeating ECHO following resolution.

8.4.8.2 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.

8.4.9 Adverse Events and Serious Adverse Events

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

8.4.9.1.1 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 the first dose of investigational products through the second safety follow-up visit **or 60 days after the last dose of investigational product(s), whichever is later,** are reported using the Events CRF.

8.4.9.1.2 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 second safety follow-up visit or 60 days after the last dose of investigational 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.

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

8.4.9.1.3 Reporting 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 and all fatal serious adverse events (regardless of causality), then these serious adverse events will be reported to Amgen. The investigator will report serious adverse events to Amgen immediately and no later than 24 hours after the investigator's awareness of the event on the Events CRF.

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 after the study has ended, then these serious adverse events will be reported to Amgen immediately and no later than 24 hours after the investigator's awareness of the event.

Serious adverse events reported after the end of 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 if the subject ends the study.

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.

8.4.9.2 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.

8.4.9.3 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 7.4). 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 awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events CRF.

8.4.9.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

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

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

8.4.9.5 Safety Monitoring Plan

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

8.4.9.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until [redacted], after the last dose of tarlatamab and [redacted] days for female study subjects and [redacted] days for female partners of male study subjects after the last dose of AMG 404.

If a pregnancy is reported, the investigator is to inform Amgen immediately and no later than 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

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

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

Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within [redacted] days of initiation of investigational product for females of childbearing potential.

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

A pregnancy test should be performed [redacted] after the last dose of tarlatamab and [redacted] days after the last dose of AMG 404.

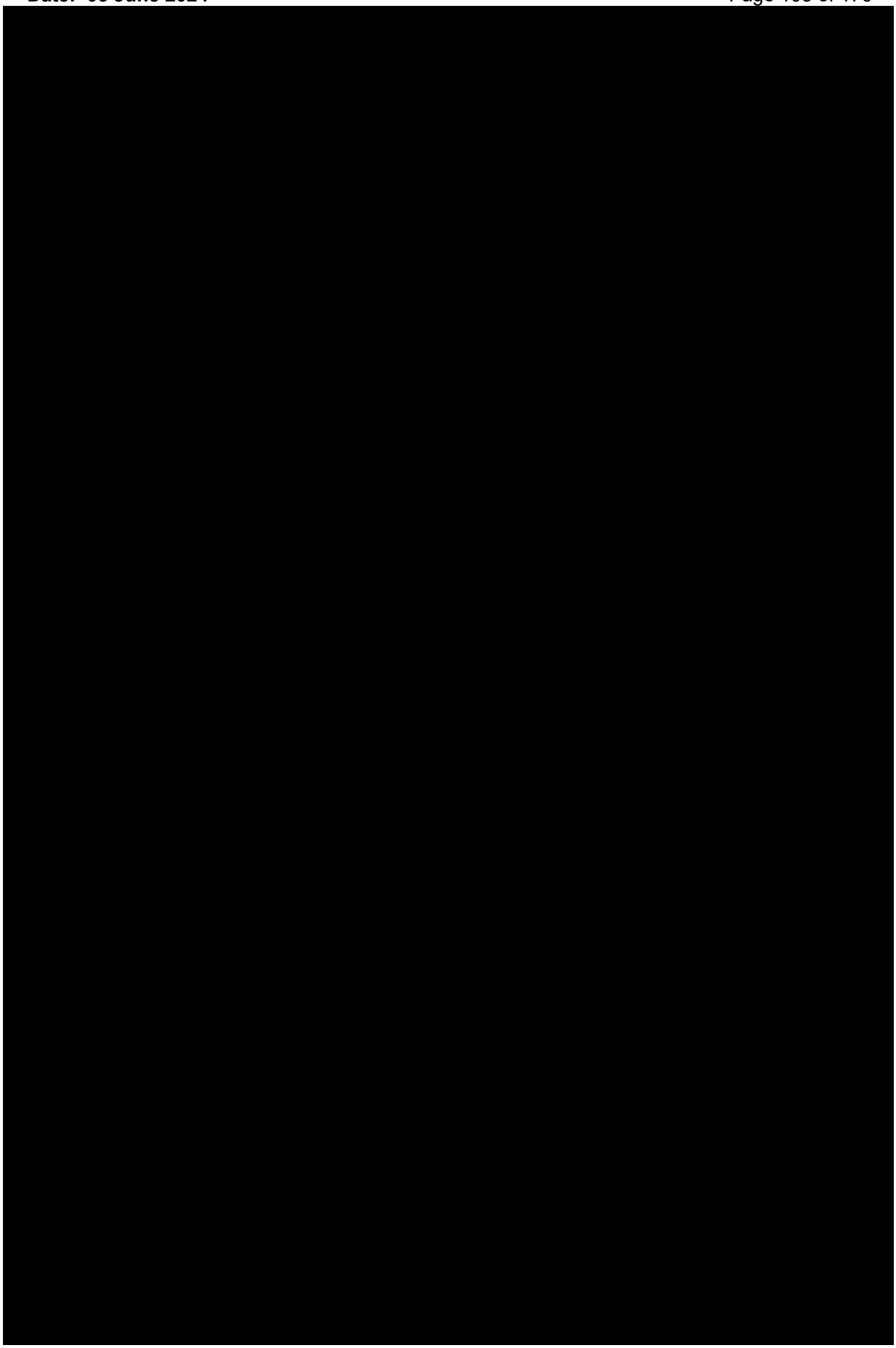
Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

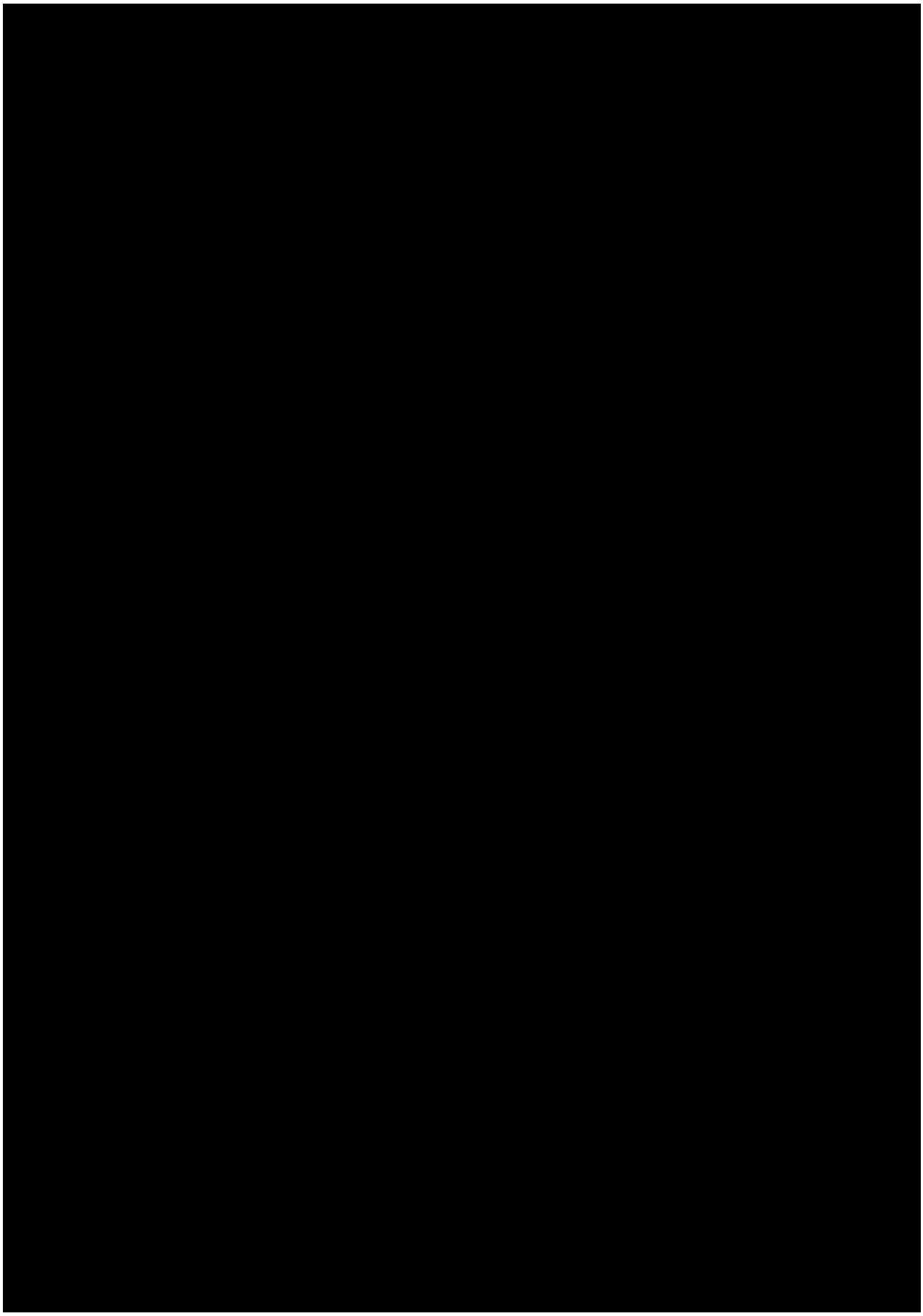
8.5 Pharmacokinetic Assessments

All subjects enrolled in the study will have PK samples assessed.

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

[redacted]





9. Statistical Considerations

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested.

9.2 Sample Size Determination

Approximately [redacted] subjects were anticipated to be enrolled in the study (up to [redacted] subjects in a dose exploration phase, and the remaining subjects enrolled in a dose expansion phase). Study enrollment ended in [redacted]. A total of [redacted] subjects were enrolled, including [redacted] subjects in Part 1, and [redacted] subjects in Part 2.

Dose Exploration Phase:

Up to 6 planned dose cohorts will be examined during dose exploration. The planned dose levels for tarlatamab with a fixed dose of AMG 404 ([redacted] mg IV [redacted] are described in Section 4.1.

Dose exploration will begin with [redacted] subjects treated at Dose Cohort Level 1. The study DLT period is [redacted] days. Once all subjects enrolled at a certain Dose Cohort Level are DLT evaluable, a DLRT meeting will be convened. Depending on observed safety data, the following may occur: 1) dose de-escalation to the next lowest Dose Cohort Level, 2) additional enrollment to the current Dose Cohort Level, or 3) dose escalation to the next highest Dose Cohort Level or initiation of enrollment in Part 2. In order to consider a certain Dose Level as the recommended phase 2 dose, at least [redacted] DLT-evaluable subjects must be enrolled at that Dose Level.

These sample sizes are based on practical considerations and are consistent with conventional oncology studies with the objective to estimate the recommended phase 2 dose and to evaluate initial safety and tolerability. The probability of observing at least 1 DLT if the true DLT rate is 10 to 30% is provided in Table 9-1 for various number of subjects.

Table 9-1. Probability of Observing at Least 1 DLT

Number of Subjects	10% DLT Rate	30% DLT Rate
[redacted]	19	55
	27	70
	34	80
	47	91
	57	96
	65	98

DLT = dose-limiting toxicity

Dose Expansion Phase:

If the sample size in the dose expansion phase of 10 (or 20). There is 65% (88%) probability of observing at least 1 adverse event with 10% incidence rate, and the 95% exact confidence interval for 20% objective response (OR) is 3% to 56% (6% to 44%).

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Enrolled	All subjects who sign the ICF
Safety	The Safety Analysis Set will consist of all subjects who received at least 1 dose of any Investigational Products. The analysis of all safety and efficacy endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set.
DLT	For the dose exploration part of the study, the analysis of DLT will be conducted on the DLT Analysis Set, defined as all subjects that are enrolled and received at least 1 dose of tarlatamab and AMG 404 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 tarlatamab and AMG 404 treatment as

	planned in cycle 1 and has been followed for safety events a minimum of [redacted] from start of treatment.
OR	The OR Analysis Set will consist of all subjects in the Safety Analysis Set who have had the opportunity to be followed for at least 8 weeks starting from day 1.
PK	The PK Analysis Set will contain all subjects who have received at least 1 dose of the Investigational Product and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

9.3.1 Covariates

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

[redacted]

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 4.5.

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 (Part 1) and formally during DLRMs, Amgen, in consultation with the site investigators, will review all available cumulative data by cohort prior to making dose escalation or dose de-escalation recommendation. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrolment and dosing decisions.

During dose expansion (Part 2), Amgen will conduct evaluations of the ongoing grade 4 or higher treatment-related **treatment emergent adverse events** to assess if the threshold for possible early trial termination has been reached. The safety interim will occur for every [redacted] subjects enrolled who have had opportunity to have at least [redacted] days of follow up since the first dose of tarlatamab. 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) Amend the protocol to potentially improve the benefit/risk for subjects (eg, increase safety monitoring, modify dose/schedule, mandate premedication)

3) Continue dose expansion without any changes.

The stopping rules use a Bayesian approach proposed by Thall (Thall et al, 1995) to terminate the study if the posterior probability that the grade 4 or higher treatment-related **treatment emergent adverse event** rate is greater than 20% is > 80%. The stopping boundaries assume a prior distribution of Beta (0.40, 1.60) are presented in Table 9-2 and the operating characteristics with pre-specified batch size of [redacted] new subjects per batch are presented in Table 9-3.

Table 9-2. 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
[redacted]	≥ 4
	≥ 6
	≥ 9
	Dose Expansion Complete

Table 9-3 Operating Characteristics with Batch Size of [redacted] 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

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 adhoc 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 **g**rade 3 rate of greater than 20% is > 80% or the posterior probability that the CRS progression to **g**rade 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**s** with regular DLRM, they may be combined.

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

Number of subjects treated with siltuximab	Trigger DLRM if severity of any CRS event treated with siltuximab progresses to Grade 5	
	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**
[redacted]	≥ 3	≥ 2
	≥ 4	≥ 2
	≥ 5	≥ 3
	≥ 6	≥ 3
	≥ 7	≥ 4
	≥ 9	≥ 4
	≥ 10	≥ 5
	≥ 11	≥ 5

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

9.4.1.2 Primary Analysis

The primary analysis for this study 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 EOT visit/procedures.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

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. 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 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	The proportion of subjects with an objective response and disease control (per modified RECIST v1.1) and 95% CI will be tabulated by planned dose level and schedule. For all subjects treated at the recommended phase 2 dose, Kaplan-Meier methods will be used to estimate for 1) duration of response (DOR), 2) OS, 3) progression-free survival (PFS) with 95% CI. For all subjects treated at the recommended phase 2 dose, Kaplan-Meier methods will be used to estimate landmarks for time to event events (eg, 6-month PFS and OS) with 95% CI.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	The analysis of DLTs will be conducted on the DLT Analysis Set. Subject incidence of DLT will be tabulated by planned dose level.
Secondary	The statistical analysis methods for other safety endpoints are below.

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 discontinuation from investigational product or other protocol-required therapies, and significant treatment emergent adverse events will also be provided. [redacted]

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 were performed as per standard of care for routine safety monitoring, rather than for 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.

9.4.2.3.9 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term for each treatment group as coded by the World Health Organization, 2018.

9.4.2.4 Other Analyses

Pharmacokinetic parameters will be determined from the concentration-time profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. [redacted]

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 using a mTPI-2 algorithm (Guo et al, 2017) with one practical modification. Consistent with conventional oncology phase 1 study designs (eg, 3+3 design) and given the imprecision with making decisions using as few as [redacted] subjects, in the instance of 1 DLT in the initial [redacted] subjects at a dose level then, as appropriate, the design allows expansion at the dose level beyond [redacted] subjects. All other dose escalation or de-escalation rules are determined strictly by the mTPI-2 algorithm as described below. 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**s** 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%, 33%).

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 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.

- [redacted] or more DLTs in ≤ [redacted] subjects
- [redacted] or more DLTs in ≤ [redacted] subjects
- [redacted] or more DLTs in ≤ [redacted] subjects
- [redacted] or more DLTs in [redacted] 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 recommended phase 2 dose will be selected from all tried dose levels that have not been previously declared to be unsafe with a DU decision according to the mTPI decision table. With this constraint, the recommended phase 2 dose will be determined as the dose level with the DLT estimate closest to the target toxicity level of 30%.

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
ACTH	adrenocorticotropic hormone
ADA-IC	anti-drug antibody related immune complexes
ADAs	anti-drug antibodies
ADCC	antibody-dependent cellular cytotoxicity
ADL	activities of daily living
ADR	adverse drug reaction
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASBMT	**American Society for Blood and Marrow Transplantation**
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASR	Annual Safety Report
AUC	area under the concentration-time curve
BCG	bacille Calmette-Guerin
BiTE®	bi-specific T-cell engager
BNP	B-Natriuretic Peptide
BP	blood pressure
CAR-T cells	**chimeric antigen receptor T cells**
CBC	complete blood count
CD3	cluster of differentiation 3
CFR	Code of Federal Regulations
CI	confidence intervals
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebral spinal fluid
CT	computed tomography
[redacted]	

Abbreviation	Explanation
CTCAE	Common Terminology Criteria for Adverse Events
D	dose de-escalation
DCR	disease control rate
DILI	drug induced liver injury
DLL3	delta-like ligand 3
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSUR	Development Safety Update Report
DOR	duration of response
E	dose escalation
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ED	extensive disease
EI	dosing interval
EDC	electronic data capture
EOI	end of infusion
EOT	End of treatment
EP	platinum-etoposide
EpCAM	epithelial cell adhesion molecule
eSAE	electronic Serious Adverse Event
EU	European Union
Fc	fragment crystallizable
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FSH	follicle stimulating hormone
FT4	free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GSO	Global Safety Officer
GLP	Good Laboratory Practice
HBcAb	anti-hepatitis B antibody
HBsAg	hepatitis B antigen

Abbreviation	Explanation
HCV	hepatitis C
HCV Ab	Hepatitis C virus antibody
HI	overdosing intervals
HIV	human immunodeficiency virus
HLE	half-life extended
HNSTD	Highest Non-Severely Toxic Dose
HR	heart rate
HUVECs	human endothelial cells
IC_{50}	half maximal inhibitory concentration
ICANS	**immune effector cell-associated neurotoxicity syndrome**
ICE	**immune effector cell-associated encephalopathy**
ICF	informed consent form
ICH	International Council for Harmonisation
ICP	**intracranial pressure**
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IL-2	interleukin-2
INN	International Nonproprietary Name
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous(ly)
LD	limited disease
LDH	lactate dehydrogenase
LH	luteinizing hormone
LI	under-dosing intervals
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MMSE	Mini Mental Status Examination
MRI	magnetic resonance imaging
mTPI	modified toxicity probability interval
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCT	National Clinical Trials

Abbreviation	Explanation
ND	not done
NSAIDs	non-steroidal anti-inflammatory drugs
OR	Objective response
OS	overall survival
PAVA	pool adjacent violators algorithm
PBL	peripheral blood leukocytes
[redacted]	
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PD-1	programmed cell death-1
PD-L1	programmed death ligand-1
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PPP	Platelet Poor Plasma
PR	partial response
Pre	pre-infusion
PT	prothrombin time
PTT	partial thromboplastin time
PTU	propylthiouracil
[redacted]	
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RO	receptor occupancy
RP2D	recommended phase 2 dose
RR	respiratory rate
RNA	ribonucleic acid
S	current dose
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
SC	subcutaneous
scFC	single chain fragment crystallizable
SCLC	Small Cell Lung Cancer
SD	stable disease
SFU	safety follow-up
SGOT	serum glutamic-oxaloacetic transaminase

Abbreviation	Explanation
SGPT	serum glutamic-pyruvic transaminase
SJS	Stevens-Johnson syndrome
SLD	sum of the longest diameters
SOI	start of infusion
SSKI	saturated solution of potassium iodide
TBL	total bilirubin
TEN	toxic epidermal necrolysis
TLS	tumor lysis syndrome
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPM	unit probability mass
US	United States
USFDA	United States food and drug administration
USPI	United States Prescribing Information
WBC	white blood cell

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

LOCAL/SAFETY LABS

Chemistry
- Sodium
- Potassium
- Chloride
- Bicarbonate or CO2
- Total protein
- Albumin
- Calcium
- Glucose
- BUN (Blood Urea Nitrogen) or Serum Urea
- Creatinine
- Total bilirubin
- Direct bilirubin
- Alkaline phos
- AST (SGOT)
- ALT (SGPT)
- Estimated CrCl, GFR, MDRD calculation

CBC with differential
- RBC
- Hemoglobin
- MCV
- Platelets
- WBC

Differentials

5-part differential:
- Lymphocytes
- Monocytes
- Eosinophils[a]
- Basophils[a]
- Total Neutrophils[a] or (Segmented neutrophils and bands/stabs]

3-part differential if unable to perform 5-part:
- Lymphocytes
- Granulocytes
- Monocytes

OR
- Lymphocytes
- Neutrophils
- Mid-cell fraction

Coagulation
- PT/INR
- Partial Thromboplastin Time (PTT) or Activated Partial Thromboplastin Time (aPTT)

Urinalysis
- Blood
- Protein
- Glucose
- Bilirubin

Endocrine safety
- Cortisol (AM sample preferred)
- TSH
- FT4
- ACTH (AM sample preferred)

Only collected at screening and EOT
- Prolactin
- FSH
- LH
- Estradiol (in females)
- Testosterone (in Males)

CENTRAL LABS

[redacted]

Other Labs:
- Tarlatamab PK
- AMG 404 PK
- Pre-dose tumor tissue (archival or fresh tumor biopsy)

[redacted]

Other safety labs
- CRP
- Ferritin
- LDH
- Uric Acid
- Phosphorus
- HIV antibody testing
- Pregnancy test (serum or urine)
- Amylase
- Lipase

Hepatitis Serology Testing
- Hep B surface antigen
- Hep C antibody
- Hep B total core antibody

[a] Local lab may report Granulocytes instead of Neutrophils, Eosinophils, and Basophils individually.
ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; AM = ante-meridiem; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CO_2 = carbon dioxide; CrCL = creatine clearance; CRP = c-reactive protein; **ctDNA = circulating tumor DNA;** EOT = end of treatment; FSH = follicle stimulating hormone; FT4 = free thyroxine; Hep B = hepatitis B; Hep C = hepatitis C; GFR = glomerular filtration rate; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; LH = luteinizing hormone; MCV = mean corpuscular volume; MDRD = modification of diet in renal disease; PT = prothrombin time; PTT = partial thromboplastin time; [redacted] PK = pharmacokinetics; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SFU = safety follow-up; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid stimulating hormone; WBC = white blood cell

If the subject is being followed for possible drug induced liver injury (DILI), the following analytes may be tested at the local laboratory depending on the clinical situation (see Section 11.7):

Table 11-2. DILI Potential Analyte Listing

Chemistry	Total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin
Hematology	Hemoglobin, Platelets, RBC Morphology, WBC Count, WBC Differential
Coagulation	PT, INR
Immunology	5 Prime Nucleotidase, Alpha-1 Antitrypsin, Antinuclear Antibodies, Anti-Smooth Muscle Antibody, Anti-Soluble Liver Ag/Liver-Pancreas Ag, Cytomegalovirus IgG Antibody, Cytomegalovirus IgM Antibody, Endomysial IgA Antibody, Epstein-Barr Virus EDA IgG Antibody, Epstein-Barr Virus NA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgM Antibody, Hepatitis A Virus IgG Antibody, Hepatitis A Virus IgM Antibody, Hepatitis B Core Antibodies, Hepatitis B Core IgM Antibody, Hepatitis B Surface Antigen, Hepatitis B Virus DNA Genotyping, Hepatitis B Virus Surface Antibody, Hepatitis C Antibodies, Hepatitis C Virus RNA Genotyping, Hepatitis D Virus Antibody, Hepatitis E IgG Antibody, Hepatitis E IgM Antibody, Herpes Simplex Virus Type 1_2 IgG AB, Herpes Simplex Virus Type 1_2 IgM AB, Human Herpes Virus 6 DNA, Human Herpes Virus 7 DNA, Human Herpes Virus 8 DNA, Immunoglobulin G, Liver Kidney AB 1, Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody
Toxicology	Acetaminophen

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

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, cohort continuation, or cohort expansion; making recommendations about non-dose escalation cohorts (eg, expanded, highest dose and/or final cohort); and evaluating safety signals for purposes of applying Dose Cohort Stopping Rules. Based on emerging safety data, the dose level review team (DLRT) will make recommendations on the day of AMG 404 administration in cycle 1 as well as the dose of tarlatamab administered. The DLRT will make recommendations on additional premedications, including the recommendation to implement additional corticosteroids (dexamethasone [redacted] mg orally [PO] 6 to 16 hours prior to the first step dose and step dose[s] in cycle 1) based on emerging results from Part D in the ongoing first-in-human (FIH) study (20160323), as well as emerging data from the current study (20200439). The DLRT will also make any recommendations on adjustments to the step-dosing schedule if necessary. Additionally, based on emerging safety data, the DRLT may make recommendations on the hospitalization requirements, including reducing or eliminating the required hospitalization time in cycle 1 or cycle 2. The required DLRT members are the Medical Monitor, Global Safety Officer (GSO), and Site **i**nvestigators. The DLRT will include actively screening and enrolling Site **i**nvestigators. The Medical Monitor, GSO, and Site **i**nvestigators are the only voting DLRT members. The following non-voting Amgen representatives may also 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 **i**nvestigator(s). A Site **i**nvestigator may identify a delegate (eg, sub-**i**nvestigator) who is listed in the Delegation of Authority. If a Site **i**nvestigator does this, the Site **i**nvestigator must provide written agreement with the designee or delegate's vote.

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

All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, electrocardiogram (ECG), vital signs, and laboratory results will be reviewed. Data will not need to be source data verified and queries will not need to be resolved prior to the DLRM.

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

DLRM recommendations to escalate to the next planned cohort, or to an intermediate cohort, must be by unanimous vote. If the voting members of the DLRT are not able to reach a unanimous recommendation on whether to escalate to the next planned cohort or to an intermediate cohort, then this should be reflected in the DLRM Memo. Other recommendations, such as expanding a cohort or lowering a dose will be made by a majority vote.

Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and 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 IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

During the course of the study, if new information becomes available that alters the benefit-risk of the study or the study drug, Amgen will follow applicable regulations to notify investigators, the IRB/IEC, and regulatory authorities, as appropriate.

The investigator will be responsible for the following:

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

Informed Consent Process

An initial sample **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 informed consent form is to be prepared in the language(s) of the potential patient population.

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

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

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the **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 informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 1.

If important new information becomes available that may be relevant to the subject's consent during their participation in the study, subjects will be reconsented.

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 30 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.

The 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 **c**ase **r**eport **f**orm (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

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

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

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, as described below.

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

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

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the **s**ponsor's systems. The **s**ponsor uses access-controlled systems to house, review and analyze subject data.

These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The **s**ponsor has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the **s**ponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

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.

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

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All

persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

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

Source Documents

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

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

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

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

Elements to include:

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

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

Study and Site Closure

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

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) by a separate protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine

whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

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

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

Definition of Adverse Event

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

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [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 overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an adverse event or serious adverse event is due to small cell lung cancer (SCLC) report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer). Note: The term “disease progression” should not be used to describe the adverse event. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

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

Definition of Serious Adverse Event

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

Other medically important serious event

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event **c**ase **r**eport **f**orm (CRF).
- The investigator must assign the following mandatory adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Did the event start prior to first dose of investigational product, other protocol-required therapies;
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product(s) and other protocol-required therapies.
  - 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 as a single event with the worst severity on the Event CRF.

- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contract research organization (CRO) in lieu of completion of the Event CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

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

The Common Terminology Criteria for Adverse Events (CTCAE), version 4 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(s) protocol-required therapies and each occurrence of each adverse event.
- The investigator is obligated to assess the relationship between investigational product(s) protocol-required therapies, study-required activity and/or procedures 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 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 his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. 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 protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen immediately and no later than 24 hours of receipt of the information.

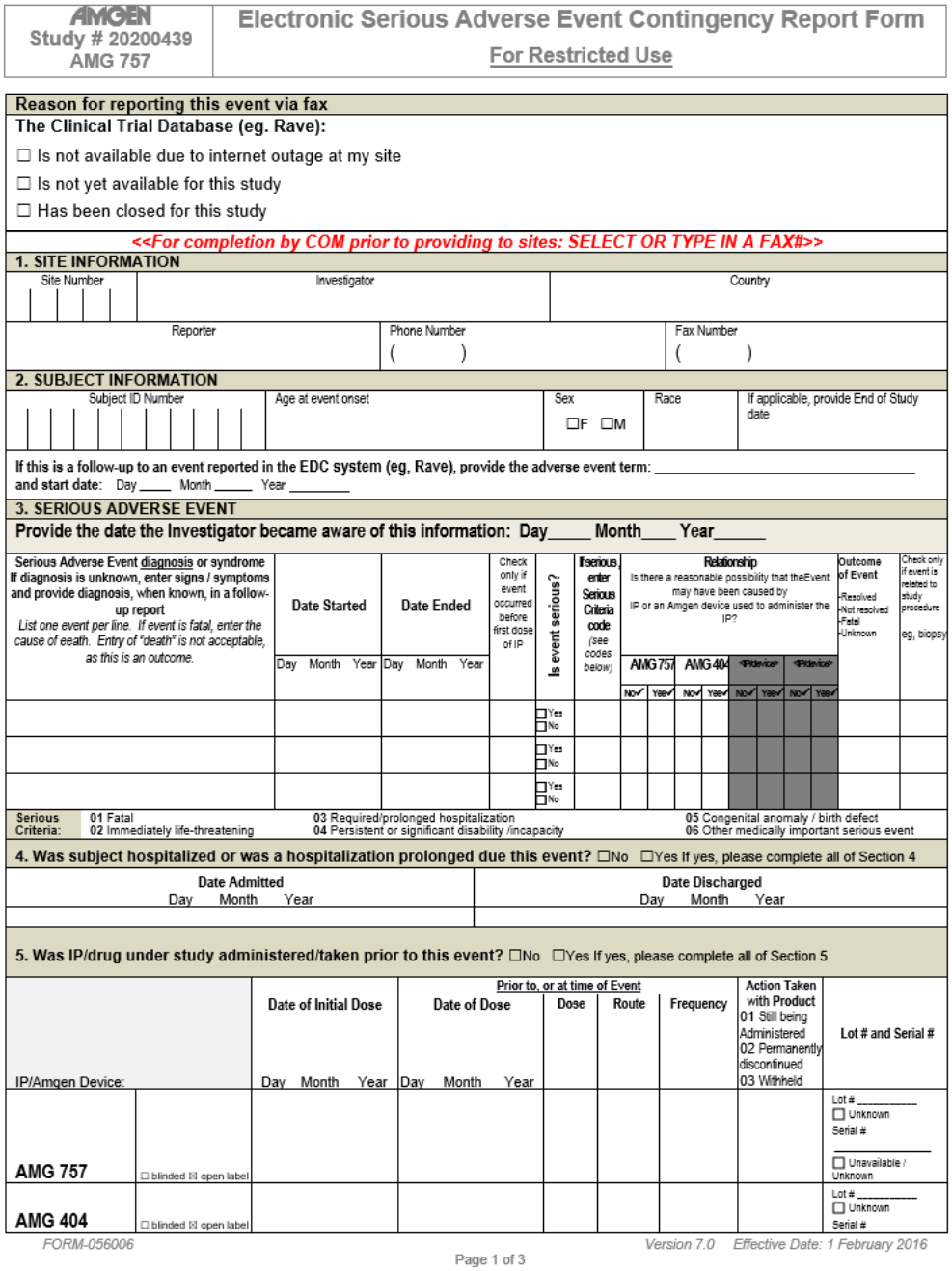
Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

- The primary mechanism for reporting serious adverse event will be the electronic data capture (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 **[**eSAE**]** Contingency Report Form) (see Figure 11-1) 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 system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 11-1).
- Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen immediately and not 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 Report Form (paper-based form)



AMGEN
Study # 20200439
AMG 757

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax
The Clinical Trial Database (eg. Rave):
☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

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

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.*	Date Started (Day Month Year)	Date Ended (Day Month Year)	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that theEvent may have been caused by IP or an Amgen device used to administer the IP? AMG 757 (No / Yes)	AMG 404 (No / Yes)	<Pdevice> (No / Yes)	<Pdevice> (No / Yes)	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

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

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

Date Admitted (Day Month Year)	Date Discharged (Day Month Year)

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

IP/Amgen Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 757	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
AMG 404	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial #

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AMGEN Study # 20200439 AMG 757	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

								☐ Unavailable / Unknown

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test / Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20200439 AMG 757	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

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

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

Male and female subjects of childbearing potential should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant (or father a child) during treatment and for [redacted], after the last dose of tarlatamab. Additionally, subjects will have pregnancy prevention requirements [redacted] following the last dose of AMG 404 (females), and an additional [redacted] following the last dose of AMG 404 (males).

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be considered not of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

A postmenopausal female is defined as:

- A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR
- A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)

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

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom **with spermicide** during treatment and for an additional [redacted] following the last dose of tarlatamab, and [redacted] days following the last dose of AMG 404

The female partner **should be made aware of the male subject's participation in the study and** should consider using a method of contraception for female subjects stated above (a female condom should not be used because there is a risk of tearing when both partners use a condom).

Note: A male subject is not required to use additional forms of contraception during the study:

- If the male's sole female partner is **post-menopausal as confirmed by her healthcare provider** or has had a bilateral tubal ligation/occlusion **or hysterectomy or bilateral oophorectomy or bilateral salpingectomy**.
- **If the male has had a vasectomy and has been medically assessed to be sterile (absence of sperm in semen).**

Collection of Pregnancy Information

<u>Female Subjects Who Become Pregnant</u>

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through [redacted] after the last dose of tarlatamab, and [redacted] after the last dose of AMG 404.

- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the site's awareness of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through [redacted] following the last dose of tarlatamab and [redacted] following the last dose of AMG 404. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment while pregnant (see Section 7.1 for details).

Male Subjects with Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional [redacted] following the last dose of tarlatamab, and [redacted] following the last dose of AMG 404 after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety 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).
- Males whose partners become pregnant during treatment and for an additional [redacted] after the last dose of tarlatamab, and [redacted] after the last dose of AMG 404 must practice sexual abstinence or use a condom through [redacted] after the last dose of tarlatamab, and [redacted] after the last dose of AMG 404.

- The investigator will attempt to obtain a signed consent 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 consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through [redacted] after the last dose of tarlatamab, and [redacted] after the last dose of AMG 404.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the investigator's awareness of the event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 226. (See Section 5.2).
- With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through [redacted] after the last dose of tarlatamab and [redacted] after the last dose of AMG 404.

Figure 11-2. Pregnancy and Lactation Notification Forms

AMGEN Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20200439

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

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (___)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

AMGEN® Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20200439

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

11.6 Appendix 6. Sample Storage and Destruction

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

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

When permitted by local regulations and if informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the small cell lung cancer, the dose response and/or prediction of response to Amgen investigational product(s) or other protocol-specified therapy, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

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

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

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

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

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

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

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

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

Table 11-3. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

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

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

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

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

If signs or symptoms recur with rechallenge, then tarlatamab and other protocol-required therapies are to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-3) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

- The event is to be reported to Amgen as a serious adverse event immediately and no later than 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate **c**ase **r**eport **f**orm (CRF) (eg, Events CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

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

Additional Clinical Assessments and Observation

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

Assessments that are to be performed during this period include:

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

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

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

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

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

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

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

11.8 Appendix 8. Performance Status According to Eastern Cooperative Oncology Group (ECOG)

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

11.9 Appendix 9. Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (Modified RECIST 1.1)

Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) are guidelines for assessing tumor burden changes in response to treatment (Eisenhauer et al, 2009). Additional patterns of response have been observed with immune-enhancing therapies, including delayed clinical response, leading to criteria modifications to capture treatment responses more accurately (Nishino et al, 2013; Wolchok et al, 2009). This study utilizes modified RECIST 1.1 criteria which applies aspects of the immune-related response criteria (including requiring confirmation of disease progression) to RECIST 1.1 as outlined below.

Modified RECIST 1.1 tumor response assessment

- All measurable and non-measurable lesions should be assessed at screening, all defined tumor assessment time points (Schedule of Assessment), and any unscheduled imaging visits.

Measurable lesions:

- Non-nodal lesions with clear borders that can be measured accurately and serially in one dimension in the axial plane (longest diameter ≥ 10 mm measured by magnetic resonance imaging/computed tomography **[**MRI/CT**]** with scan slice thickness ≤ 5 mm).
- Nodal lesions with the longest diameter perpendicular to the long axis (short axis) ≥ 15 mm on MRI/CT.
- Must exclude simple cysts, pleural/pericardial effusions and ascites.

Non-measurable lesions:

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm but < 15 mm short axis) are considered non-measurable and characterized as non-index lesions.
- Other examples of non-measurable lesions include:
    - Lesions with prior local treatment:
        - Tumor lesions situated in a previously irradiated area, or an area subject to other loco-regional therapy, should not be considered measurable unless there has been demonstrated progression in the lesion.
    - Biopsied lesions
    - Categorically, clusters of small lesions, bone lesions, inflammatory breast disease, and leptomeningeal disease are non-measurable. See Imaging Procedural Manual provided by the central imaging core laboratory for additional guidance.

Index lesions and measurable tumor burden:

- Index lesions:
    - Measurable lesions (≤ 5 lesions per organ, ≤ 10 total) selected at baseline on the basis of
        - Size and suitability for accurate repeated measurements by imaging.
        - Representative of the subject's tumor burden, all organs involved and overall disease status

Non-index lesions:

- All measurable lesions not selected as index lesions and non-measurable lesions
- Non-index lesions will be qualitatively evaluated
    - Values: 'Present', 'absent' or 'unequivocal progression'.
- Other definitions
    - Unable to evaluate (UE): Any lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point
    - Not Available (NA): Scan not available
    - Not Done (ND): Radiologic imaging was not performed at this time point to evaluate the index lesions

Index lesion response:

- At baseline and all subsequent tumor assessments, measurable tumor burden is the sum of the longest diameters (SLD) of all index lesions
- Complete Response (CR) – disappearance of all measurable lesions
    - Pathologic lymph nodes must have reduction in short axis to < 10 mm
- Partial Response (PR) – decrease of 30% or greater in tumor burden compared with baseline
- Stable Disease (SD) - not meeting the criteria for CR, PR, or progressive disease
- Progressive Disease – increase of 20% or greater in tumor burden compared with nadir, or the appearance of one or more new lesions

Non-index lesion response:

- CR – disappearance of all non-index lesions
    - Pathologic lymph nodes must have reduction in short axis to < 10 mm
- SD – persistence of one or more non-index lesions, not meeting the criteria for CR or progressive disease
- Progressive disease – unequivocal progression of existing non-index lesions, or the appearance of one or more new lesions

Overall response:

- CR
  - Complete disappearance of all lesions
    - Pathologic lymph nodes must have reduction in short axis to < 10 mm
  - Confirmation scan required - repeat, consecutive assessment no less than 4 weeks from the date of the first documented response
  - CR is dated at time of confirmation scan
- PR
  - Decrease in tumor burden ≥ 30% relative to baseline, or
  - Complete disappearance of all index lesions with presence of non-index lesions
  - Confirmation scan required - repeat, consecutive assessment no less than 4 weeks from the date of the first documented response
  - PR is dated at time of confirmation scan
- SD
  - Index lesions not meeting criteria for CR, PR or progressive disease, or
  - In subjects with only non-index disease, persistence of one or more non-index lesions
- Progressive Disease
  - Radiologic detection of ≥ 20% increase in tumor burden relative to nadir and at least 5 mm absolute increase, or
  - Unequivocal progression of non-index lesions, or
  - The presence of new lesions
  - Confirmation scan required - repeat, consecutive assessment [redacted] from the date of the first documented response
    - Radiographic progressive disease is confirmed at repeat imaging [redacted] if:
      - Tumor burden remains increased by ≥ 20% and at least 5 mm absolute increase relative to nadir, or
      - Unequivocal progression of non-index lesions is observed, or
      - New lesions are present
- Subjects with a global deterioration of health status requiring discontinuation of treatment prior to radiologic confirmation of disease progression should have the reason for treatment discontinuation classified as ‘clinical disease progression’ not ‘radiographic progressive disease’. Every effort should be made to radiologically confirm progression even after discontinuation of treatment.

Summary of Measurement and Tumor Response Assessment Based on Modified RECIST 1.1	
Measurable lesions	• Non-nodal lesions: ≥ 10 mm (unidimensional measurement) • Pathologic lymph nodes: longest diameter short axis ≥ 15 mm
Measurement of each lesion	• Non-nodal lesions: The longest diameter (mm) in the axial plane • Pathologic lymph nodes: short axis (mm)
Tumor burden	• Sum of the longest diameters (SLD) of all index lesions • Up to 5 lesions per organ, up to 10 total
Response assessment: index lesions (calculated from % change in tumor burden)	• CR: Disappearance of all lesions • Pathologic lymph nodes short axis < 10 mm • PR: ≥ 30% decrease from baseline • SD: Does not meet criteria for CR, PR or progressive disease. • Progressive disease: ≥ 20% increase (and ≥ 5 mm absolute increase) from nadir
Response assessment: non-index lesions	• CR: Disappearance of all lesions • Pathologic lymph nodes short axis < 10 mm • SD: Persistence of one or more non-index lesion(s) • Progressive disease: Unequivocal progression of existing non-index lesions
New Lesions	The presence of new lesion(s) defines progression
Confirmation	Confirmation by subsequent assessment after ≥4 weeks required for CR, PR and progressive disease.

Summary of Modified RECIST 1.1 Overall Response Assessment			
Index lesions (tumor burden)[a], %	Non-Index lesions	New lesions	Overall Response using modified RECIST 1.1
↓ 100%	Absent	Absent	CR[b]
None[d]	Absent	Absent	CR[b]
↓ 100%	Present	Absent	PR[b]
↓ ≥ 30%	Absent/Present	Absent	PR[b]
↓ < 30% to ↑ < 20%	Absent/Present	Absent	SD
None[d]	Present	Absent	SD
↑ ≥ 20%	Any	Any	Progressive disease[c]
Any	Unequivocal progression	Any	Progressive disease[c]
Any	Any	Present	Progressive disease[c]
NA/ND/UE	Absent/Present	Absent	UE
None[d]	NA/ND/UE	Absent	UE

CR = complete response; NA = not available; ND = not done; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; **SD = stable disease;** UE = unable to evaluate

[a] Decrease assessed relative to baseline. Increase assessed relative to nadir.

[b] Response: CR and PR require a confirmation assessment after ≥ 4 weeks, may also wait until the next scheduled imaging

[c] Progression: Progressive disease requires a confirmation assessment [redacted]

[d] Subjects with non-index lesions only

11.10 Appendix 10. Schedule of Activities:

Table 11-4. List of Schedule of Activities Tables

Quick link to Schedule of Activities	Table Title
Table 11-5	One-Step Dosing – Cycle 1 only (AMG 404 Administered [redacted]
Table 11-6	One-Step Dosing – Cycle 1 only (AMG 404 Administered [redacted]
Table 11-7	One-Step Dosing – Cycle 1 only (AMG 404 Administered [redacted]
Table 11-8	Cycle 2 and Beyond (AMG 404 Administered on [redacted] in Cycle 1)
Table 11-9	Cycle 2 and Beyond (AMG 404 Administered on [redacted] in Cycle 1)

Table 11-5. Schedule of Activities: One-Step Dosing – Cycle 1 Only (AMG 404 Administered [redacted]

STUDY PERIOD/ TREATMENT CYCLE	SCR[a]	Cycle 1 only																					
WEEK[b]	-3 to -1	1									2						3						4
DAY[b]	[redacted]																						
HOUR (relative to infusion)[d]		Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	96	Pre 757	EOI 757	2	6	24	48	Pre 757	EOI 757	2	6	24	48	168
General/Safety Assessments																							
Informed consent	X																						
Clinical Evaluation[e]	X	X						X	X	X	X				X	X	X				X	X	X
Vital signs, pulse ox[f]	X	X	X	X	X		X[f]				X	X		X[f]		X	X	X		X[f]		X	X
12-lead ECG[g]	X			X	X							X						X					
ECHO or MUGA	X																						
Adverse event review			←==========→																				
Serious adverse event 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		
Chemistry panel[h]	X	X					X	X	X	X	X				X	X	X				X	X	X
Lipase and Amylase	X	X																					
Urinalysis	X																						
Serum/urine pregnancy test[i]	X	X																					
Safety endocrine panel[j]	X																						
CRP		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
HBsAg, HBcAb, HCV Ab, HIV	X																						

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Footnotes described after **Table 11-9**

Table 11-5. Schedule of Activities: One-Step Dosing – Cycle 1 Only (AMG 404 Administered [redacted]

STUDY PERIOD/ TREATMENT CYCLE	SCR[a]	Cycle 1 only																			
WEEK[b]	-3 to -1	1									2						3					4
DAY[b]	[redacted]																					
HOUR (relative to infusion)[d]		Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	96	Pre 757	EOI 757	2	6	24	48	Pre 757	EOI 757	2	6	24	48	168
Central and Biomarker Laboratory Tests																							
[redacted]																							
Study Drug Administration																							
Tarlatamab IV infusion[t]	[redacted]																						
AMG 404 IV infusion[t]																							

Footnotes described after **Table 11-9**

Table 11-5. Schedule of Activities: One-Step Dosing – Cycle 1 Only (AMG 404 Administered [redacted]

STUDY PERIOD/ TREATMENT CYCLE	SCR[a]	Cycle 1 only																				
WEEK[b]	-3 to -1	1									2						3					4
DAY[b]	[redacted]																					
HOUR (relative to infusion)[d]		Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	96	Pre 757	EOI 757	2	6	24	48	Pre 757	EOI 757	2	6	24	48	168
Study Drug Administration (continued)																							
Dexamethasone or equivalent[u]				X							X						X						
IV Hydration[v]					X							X						X					
Hospital stay[w]		←==========→									←==========→						←==========→						
Other Assessments																							
MRI Brain[x]	X																						
Radiological imaging and tumor burden assessment[y]	X																						

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Footnotes described after **Table 11-9**

Table 11-6. Schedule of Activities: One-Step Dosing – Cycle 1 Only (AMG 404 Administered [redacted]

STUDY PERIOD/ TREATMENT CYCLE	SCR[a]	Cycle 1 only																					
WEEK[b]	-3 to -1	1							2[c]								3						4
DAY[b]	[redacted]																						
HOUR (relative to infusion)[d]		Pre 757	EOI 757	2	6	24	48	96	Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	Pre 757	EOI 757	2	6	24	48	168
General/Safety Assessments																							
Informed consent	X																						
Clinical Evaluation[e]	X	X				X	X	X	X						X	X	X				X	X	X
Vital signs, pulse ox[f]	X	X	X		X[f]				X	X	X	X		X[f]		X	X	X		X[f]		X	X
12-lead ECG[g]	X	X	X									X						X					
ECHO or MUGA	X																						
Adverse event review			←==========																				==========→
Serious adverse event 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		
Chemistry panel[h]	X	X			X	X	X	X	X						X	X	X				X	X	X
Lipase and Amylase	X	X																					
Urinalysis	X																						
Serum/urine pregnancy Test[i]	X	X																					
Safety endocrine panel[j]	X																						
CRP		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
HBsAg, HBcAb, HCV Ab, HIV	X																						
Central and Biomarker Laboratory Tests																							
[redacted]																							

Footnotes described after **Table 11-9**

Table 11-6. Schedule of Activities: One-Step Dosing – Cycle 1 Only (AMG 404 Administered Day 8)

STUDY PERIOD/ TREATMENT CYCLE	SCR[a]	Cycle 1 only																			
WEEK[b]	-3 to -1	1							2[c]							3						4
DAY[b]	[redacted]																					
HOUR (relative to infusion)[d]		Pre 757	EOI 757	2	6	24	48	96	Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	Pre 757	EOI 757	2	6	24	48	168
Central and Biomarker Laboratory Tests (continued)																							
[redacted]																							
Study Drug Administration																							
Tarlatamab IV infusion[t]	[redacted]																						
AMG 404 IV infusion[t]																							
Dexamethasone or equivalent[u]		X									X						X						
IV Hydration[v]			X									X						X					
Hospital stay[w]		←==========→							←==========→								←==========→						

Footnotes described after **Table 11-9**

Table 11-6. Schedule of Activities: One-Step Dosing – Cycle 1 Only (AMG 404 Administered Day 8)

STUDY PERIOD/ TREATMENT CYCLE	SCR[a]	Cycle 1 only																				
WEEK[b]	-3 to -1	1							2[c]							3						4
DAY[b]																						
HOUR (relative to infusion)[d]		Pre 757	EOI 757	2	6	24	48	96	Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	Pre 757	EOI 757	2	6	24	48	168
Other Assessments																							
MRI Brain[x]	X																						
Radiological imaging and tumor burden assessment[y]	X																						

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Footnotes described after **Table 11-9**

Table 11-7. Schedule of Activities: One-Step Dosing – Cycle 1 Only (AMG 404 Administered [redacted]

STUDY PERIOD/ TREATMENT CYCLE	SCR[a]	Cycle 1 only																						
WEEK[b]	-3 to -1	1							2[c]						3									4
DAY[b]	[redacted]																							
HOUR (relative to infusion)[d]		Pre 757	EOI 757	2	6	24	48	96	Pre 757	EOI 757	2	6	24	48	Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	168
General/Safety Assessments																								
Informed consent	X																							
Clinical Evaluation[e]	X	X				X	X	X	X				X	X	X						X	X	X	
Vital signs, pulse ox[f]	X	X	X		X[f]		X	X	X	X		X[f]		X	X	X	X	X		X[f]		X	X	
12-lead ECG[g]	X	X	X							X								X						
ECHO or MUGA	X																							
Adverse event review			←==========																					→
Serious adverse event 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			
Chemistry panel[h]	X	X			X	X	X	X	X				X	X	X						X	X	X	
Lipase and Amylase	X	X																						
Urinalysis	X																							
Serum/urine pregnancy Test[i]	X	X																						
Safety endocrine panel[j]	X																							
CRP		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	
HBsAg, HBcAb, HCV Ab, HIV	X																							
Central and Biomarker Laboratory Tests																								
[redacted]																								

Footnotes described after **Table 11-9**

Table 11-7. Schedule of Activities: One-Step Dosing – Cycle 1 Only (AMG 404 Administered Day 15)

STUDY PERIOD/ TREATMENT CYCLE	SCR[a]	Cycle 1 only																				
WEEK[b]	-3 to -1	1							2[c]						3							4
DAY[b]	[redacted]																					
HOUR (relative to infusion)[d]		Pre 757	EOI 757	2	6	24	48	96	Pre 757	EOI 757	2	6	24	48	Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	168
Central and Biomarker Laboratory Tests (continued)																							
[redacted]																							
Study Drug Administration																							
Tarlatamab IV infusion[t]	[redacted]																						
AMG 404 IV infusion[t]																							
Dexamethasone or equivalent[u]		X							X								X						
IV Hydration[v]			X							X								X					
Hospital stay[w]		←==========→							←==========→						←==========→								
Other Assessments																							
MRI Brain[x]	X																						
Radiological imaging and tumor burden assessment[y]	X																						

Footnotes described after **Table 11-9**

Table 11-8. Schedule of Activities: Cycle 2 and Beyond (If AMG 404 was Administered on [redacted] or 8 in Cycle 1)

STUDY PERIOD/ TREATMENT CYCLE	Cycle 2																Q cyc[bb]		Q2 cyc	EOT[hh]	SFU-1[ee]	SFU-2[ff]	LTFU[aa]
WEEK[b]	1									2[c]	3					4	1	3	1				
DAY[b]	[redacted]																						
HOUR (relative to infusion)[d]	Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	96	168	Pre 757	EOI 757	2	6	24	48	168						
General/Safety Assessments																							
Clinical Evaluation[e]	X						X	X	X	X	X				X	X	X	X	X		X	X	X	
Vital signs, pulse ox[f]	X	X	X	X		X[f]		X	X	X	X	X		X[f]		X	X	X	X		X	X	X	
12-lead ECG[g]				X								X						X[cc]	X[cc]					
ECHO or MUGA																								
Adverse event review		←==========															========== →							
Serious adverse event review	←==========																========== →							
Prior/concomitant medication	←==========																========== →							
Local Laboratory Assessments																							
CBC with differential	X						X	X		X	X				X	X	X	X	X		X	X	X	
Coagulation	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	X	
Lipase and Amylase	X																	X				X		
Urinalysis																				X				
Serum/urine pregnancy Test[i]	X																	X				X	X	
Safety endocrine panel[j]	X																	X			X	X		
CRP	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		
Central and Biomarker Laboratory Tests																								
[redacted]																								

Footnotes described after **Table 11-9**

Table 11-8. Schedule of Activities: Cycle 2 and Beyond (If AMG 404 was Administered on [redacted] in Cycle 1)

STUDY PERIOD/ TREATMENT CYCLE	Cycle 2																	Q cyc[bb]		Q2 cyc	EOT[hh]	SFU-1[ee]	SFU-2[ff]	LTFU[aa]
WEEK[b]	1									2[c]	3						4	1	3	1				
DAY[b]	[redacted]																							
HOUR (relative to infusion)[d]	Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	96	168	Pre 757	EOI 757	2	6	24	48	168							
[redacted]																								
General/Safety Assessments																								
[redacted]																								
Tarlatamab PK collection[p]			X	X		X	X	X		X	X	X		X	X	X	X	X[q]						
AMG 404 PK collection[p]	X	X									X							X[r]					X	
Study Drug Administration																								
Tarlatamab IV infusion[t]	[redacted]																							
AMG 404 IV infusion[t]																								
Hospital stay[w]	←==========→										←==========→													
Other Assessments																								
MRI Brain[x]																								
Radiological imaging and tumor burden assessment[y]																				X	X[z]	X[z]		X[dd]
Survival Status and subsequent cancer therapy[aa]																								X

Footnotes described after **Table 11-9**

Table 11-9. Schedule of Activities: Cycle 2 and Beyond (If AMG 404 was Administered on [redacted] in Cycle 1)

STUDY PERIOD/ TREATMENT CYCLE	Cycle 2																	Q cyc[bb]		Q2 cyc	EOT[hh]	SFU-1[ee]	SFU-2[ff]	LTFU[aa]
WEEK[b]	1							2[c]	3								4	1	3	1				
DAY[b]	[redacted]																							
HOUR (relative to infusion)[d]	Pre 757	EOI 757	2	6	24	48	96	168	Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	168							
General/Safety Assessments																								
Clinical Evaluation[e]	X				X	X	X	X	X						X	X	X	X	X		X	X	X	
Vital signs, pulse ox[f]	X	X		X[f]		X	X	X	X	X	X	X		X[f]		X	X	X	X		X	X	X	
12-lead ECG[g]		X										X						X[cc]	X[cc]					
ECHO or MUGA																								
Adverse event review		←==========															========== →							
Serious adverse event review	←==========																========== →							
Prior/concomitant medication	←==========																========== →							
Local Laboratory Assessments																								
CBC with differential	X				X	X		X	X						X	X	X	X	X		X	X	X	
Coagulation	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	X	
Lipase and Amylase	X																	X				X		
Urinalysis																				X				
Serum/urine pregnancy Test[i]	X																	X				X	X	
Safety endocrine panel[j]	X																	X			X	X		
CRP	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		
Central and Biomarker Laboratory Tests																								
[redacted]																								

Footnotes described after **Table 11-9**

Table 11-9. Schedule of Activities: Cycle 2 and Beyond (If AMG 404 was Administered on [redacted] in Cycle 1)

STUDY PERIOD/ TREATMENT CYCLE	Cycle 2																	Q cyc[bb]		Q2 cyc	EOT[hh]	SFU-1[ee]	SFU-2[ff]	LTFU[aa]
WEEK[b]	1							2[c]	3								4	1	3	1				
DAY[b]	[redacted]																							
HOUR (relative to infusion)[d]	Pre 757	EOI 757	2	6	24	48	96	168	Pre 404	EOI 404	Pre 757	EOI 757	2	6	24	48	168							
[redacted]																								
Tarlatamab PK collection[p]	X	X		X	X	X		X			X	X		X	X	X	X	Xq						
AMG 404 PK collection[p]									X	X									X[r]				X	
Study Drug Administration																								
Tarlatamab IV infusion[t]	[redacted]																							
AMG 404 IV infusion[t]																								
Hospital stay[w]	←==========→								←==========→															
Other Assessments																								
MRI Brain[x]																								
Radiological imaging and tumor burden assessment[y]																				X	X[z]	X[z]		X[dd]
Survival Status and subsequent cancer therapy[aa]																								X

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Abbreviations used: 0 = Hour zero; when Tarlatamab is infused; ACTH = adrenocorticotropic hormone; BP = blood pressure; C = cycle; C1[redacted] = cycle 1 [redacted] CBC = complete blood count; CNS = central nervous system; CRP = C-reactive protein; CT = computed tomography; ctDNA = cell-free tumor DNA; CTC = circulating [redacted] ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOI = end of infusion; EOT = end of treatment; FFPE = formalin-fixed paraffin-embedded; FSH = follicle stimulating hormone; FT4 = free thyroxine; HBcAb = anti-hepatitis B antibody; HBsAg = hepatitis B antigen; HCV = hepatitis C; HIV = human immunodeficiency virus; HR = heart rate; IGF-1 = insulin-like growth factor 1; IV = intravenous; LH = luteinizing hormone; MUGA = multigated acquisition; LDH = lactate dehydrogenase; LTFU = long-term follow-up; MRI = magnetic resonance imaging; [redacted] PD = progressive disease; PK = pharmacokinetic; Pre = pre-infusion; Q cyc = every cycle; Q2 Cyc = every 2 cycles; RECIST = response evaluation criteria in solid tumors; RR = respiratory rate; SCR = screening; SFU = safety follow-up; SOI = start of infusion; TLS = tumor lysis syndrome; TSH = thyroid stimulating hormone

a All screening procedures should be performed within [redacted] prior to cycle 1 [redacted] dosing.

b Each visit week and day is relative to [redacted] of each cycle. cycle 1 and 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 See Section 6.2.1.3 for more details regarding Step Dosing.

d
- End of infusion (EOI) assessments or procedures are to be completed immediately after infusion of tarlatamab. EOI indicates the time when the investigational product 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 [redacted] dosing where laboratory assessments that were done within 48 hours prior to infusion do not need to be repeated).
- All assessments and procedures should be collected at the exact nominal time point as noted in the Schedule of Assessments. 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.

e Clinical evaluation including physical exam, ECOG, weight and neurological exams, writing test, and mini-mental status exams (neurology specialty consultation service as clinically indicated). Mini mental status exams and writing test are required on [redacted] (if [redacted] clinical evaluation required per dosing regimen), [redacted] (may be performed if clinically indicated on [redacted]) in cycle 1. Mini mental status exam and writing test may be performed in cycle 2 and beyond at the investigator's discretion. Performed at screening only: demographics, medical history, and height. Clinical evaluation should be completed within 6 hours prior to the first dose of tarlatamab.

f Vital signs (BP, HR, RR, temp) and pulse oximetry will be assessed. Vitals will be taken pre-AMG 404 infusion and at AMG 404 EOI. [redacted] For each tarlatamab-infusion for the first 2 cycles (during the hospitalization period) vital signs should be assessed as detailed in Section 8.4.1.

g ECGs will be collected once and considered safety ECGs. ECGs should be collected prior to blood draws when assessments are conducted at the same nominal time point (pre-infusion timepoints for tarlatamab and AMG 404 may be collected 15 minutes prior to infusion, post-infusion time points for tarlatamab may be collected ± 15 minutes of indicated time point). See Section 8.4.5.

h For cycles 1 and 2 only, please collect LDH, phosphorus, and uric acid along with the chemistry panel for TLS monitoring.

i Serum pregnancy test at screening; serum or urine pregnancy test monthly until [redacted] from the last investigational product (tarlatamab or AMG 404) dose. Additionally, a pregnancy test at [redacted] after last dose of AMG 404.

j Safety endocrine panels: ACTH, cortisol, TSH, and FT4 will be evaluated at screening, [redacted] of every cycle starting with cycle 2, EOT, and SFU-1. Prolactin, FSH, LH, testosterone (in males) and estradiol (in females) will be evaluated only at screening, EOT, and as clinically indicated.

[redacted]

m A tumor biopsy is required at screening if patient has received any treatment prior to participating into this study and biopsy can be performed safely as determined by the investigators. Tumor tissue (archival or fresh biopsy) must be available. Subjects must consent to allow the acquisition of FFPE material (block or unstained slides) by study personnel.

[redacted]

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

r AMG 404 PK samples to be collected at pre-infusion and end of infusion in cycles 3, 5, 7, 9, and 11 and at pre-infusion in cycles 4, 6, 8, 10, and 12.

[redacted]

[redacted]

u Dexamethasone [redacted] mg IV (or equivalent dose of other corticosteroids) will be administered within 1 hour prior to all tarlatamab doses, in week 1 and step doses of tarlatamab in cycle 1 only.

v Refer to Section 6.1.4 for administration details.

[redacted]

x All subjects must have MRI/CT of the brain performed within 21 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.

y [redacted]

- Tumor burden assessments will be performed based on modified RECIST 1.1 guidelines (see Section 11.9).

[redacted]

aa LTFU will be conducted every 3 months (± 2 weeks) for 1 year 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 only. If the investigator becomes aware of serious adverse events suspected to be related to investigational product or any fatal adverse event (regardless of causality) after the protocol-required reporting period (as defined in Section 8.4.9.1.3) is complete, 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 Event eCRF.

bb Assessments to be completed at specified timepoint beginning with cycle 3 and at each subsequent cycle unless otherwise specified.

cc For cycles 3 and 4 only: please collect ECG post-tarlatamab infusion. No further ECG's are collected after cycle 4.

dd For subjects who discontinued treatment for any reason other than confirmed PD, every effort should be made to perform radiographic imaging (CT/MRI) of the chest, abdomen, pelvis, and all other known sites of disease every 3 months until documentation of confirmed PD per modified RECIST 1.1, clinical progression, start of new anticancer therapy, or up to 12 months after the first dose of tarlatamab, whichever occurs first.

ee The first safety follow-up visit should be completed [redacted] from the last dose (tarlatamab or AMG 404).

ff The second safety follow-up visit should be completed [redacted] after the last dose of AMG 404 or prior to initiation of other therapy, whichever occurs first.

[redacted]

hh After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.9.1.3 for additional details.

Amendment 5

Protocol Title: A Phase 1b Study Evaluating the Safety and Efficacy of AMG 757 in Combination with AMG 404 in Subjects with Small Cell Lung Cancer (SCLC)

Amgen Protocol Number AMG 757, AMG 404, 20200439

EudraCT number: 2020-005957-26

NCT Number: NCT04885998

Amendment Date: 05 June 2024

Rationale:

This protocol is primarily being amended to align with the latest updates to the Core Risks and Discomforts section of the informed consent form (ICF).

The following changes were also incorporated into the protocol:

- Updated the version number and date of the amendment.
- Updated the safety follow-up period for tarlatamab throughout the protocol, to [redacted] (previously [redacted]) following the last dose.
- Updated the second safety follow-up period for AMG 404 throughout the protocol, to [redacted] (previously [redacted]) following the last dose.
- Updated the timeframe for using contraception following the last dose of tarlatamab throughout the protocol, which has now been updated to [redacted] for female subjects (previously [redacted]) and male subjects and their female partners (previously [redacted]).
- Added new Section 2.3.3.1.1.2, Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) and its support care and risk management guidelines in the new Section 6.8.2, since ICANS has been identified as a common side-effect of tarlatamab in the Core Risks and Discomforts section of the informed consent form (ICF).
- Added language to Sections 8.4.9.1.1, Adverse Events and 8.4.9.1.2, Serious Adverse Events, to clarify that investigator is responsible for collection of adverse

events and serious adverse events, 30 days after the last dose of investigational product(s) or after the second safety follow-up, whichever is later.

- Updated Section 11.5, Appendix 5, Contraceptive Guidance and Collection of Pregnancy and Lactation Information for:
    - barrier contraceptive methods for female subjects and female partners of male subjects.
    - condoms with spermicide for male subjects
    - conditions for not using additional forms of contraception for male subjects during the study.
- Administrative, abbreviations, numbering, grammatical and editorial changes have been made throughout the protocol for clarification.

Amendment 4

Protocol Title: A Phase 1b Study Evaluating the Safety and Efficacy of AMG 757 in Combination with AMG 404 in Subjects with Small Cell Lung Cancer (SCLC)

Amgen Protocol Number AMG 757, AMG 404, 20200439

EudraCT number: 2020-005957-26

NCT Number: NCT04885998

Amendment Date: 10 November 2023

Rationale:

This protocol is mainly being amended to specify the conditions to be met for the continuation of tarlatamab treatment in subjects with radiologic disease progression, who continue to have clinical benefits as per the investigator's judgement. A new section (Section 7.2) has been added to elaborate the conditions to be met and language is being included throughout to update/clarify the protocol. The following changes were also incorporated into the protocol:

- Updated the key sponsor contact as [redacted] MD and also updated the relevant contact details.
- Added language to the rationale in Section 1.1 and Section 2.1 to clarify that AMG 404 has been evaluated as a monotherapy agent.
- Added footnotes in the schedule of assessment tables (Table 1-2, Table 11-8 and 11-9) to clarify the reporting requirements of serious adverse events.
- Removed sucrose-mediated renal impairment as a potential safety concern for tarlatamab and deleted language related to this throughout the protocol.
- Deleted language related to first-in-human study in Section 4.4.1.1.
- Clarified the requirements for recording and reporting of serious adverse events in Section 8.4.9.1.2 and Section 8.4.9.1.3 and changes associated with this were updated throughout the protocol.
- Clarified the timing for collecting pregnancy and lactation details for female subjects and female partners of male subjects after tarlatamab treatment in Section 8.4.9.6 and associated changes were updated throughout the protocol.
- Administrative, grammatical and editorial changes have been made throughout the protocol for clarification.

Amendment 3

Protocol Title: A Phase 1b Study Evaluating the Safety and Efficacy of AMG 757 in Combination with AMG 404 in Subjects with Small Cell Lung Cancer (SCLC)

Amgen Protocol Number Tarlatamab 20200439

Amendment Date: 04 April 2023

[redacted]

Amendment 2

Protocol Title: A Phase 1b Study Evaluating the Safety and Efficacy of AMG 757 in Combination with AMG 404 in Subjects with Small Cell Lung Cancer (SCLC)

Amgen Protocol Number AMG 757, AMG 404, 20200439

EudraCT number: 2020-005957-26

NCT Number: NCT04885998

Amendment Date: 28 January 2022

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. Language is being included throughout to update/clarify the protocol. Changes including, but not limited to, the following were 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, and safety stopping rules were included
- Updated schedule of assessment (SOA) to exclude antineutrophil cytoplasmic antibodies (ANCA)/antinuclear antibody (ANA) testing as a clinical test; to modify fresh tumor biopsies language to allow biopsies on subjects who provide consent at the end of cycle 2 and end of treatment (EOT); and to clarify that safety endocrine panels are to be evaluated day 1 of every cycle starting with cycle 2
- Updated the SOA timepoints for the electrocardiogram (ECG), Coagulation, Lipases and amylase, C reactive protein (CRP), and ferritin assessments
- Updated AMG 757 and AMG 404 background clinical experience and key safety information sections, and AMG 757 toxicology section to reflect latest version of the Investigator's Brochure (IB)
- Updated restarting AMG 757 dosing rules to allow resuming of dosing if the toxicities resolve to grade $\leq$ 1 or return to subjects' baseline values within 3 weeks, instead of 4 weeks
- Update end of study section to increase the total study duration from 12 to 24 months

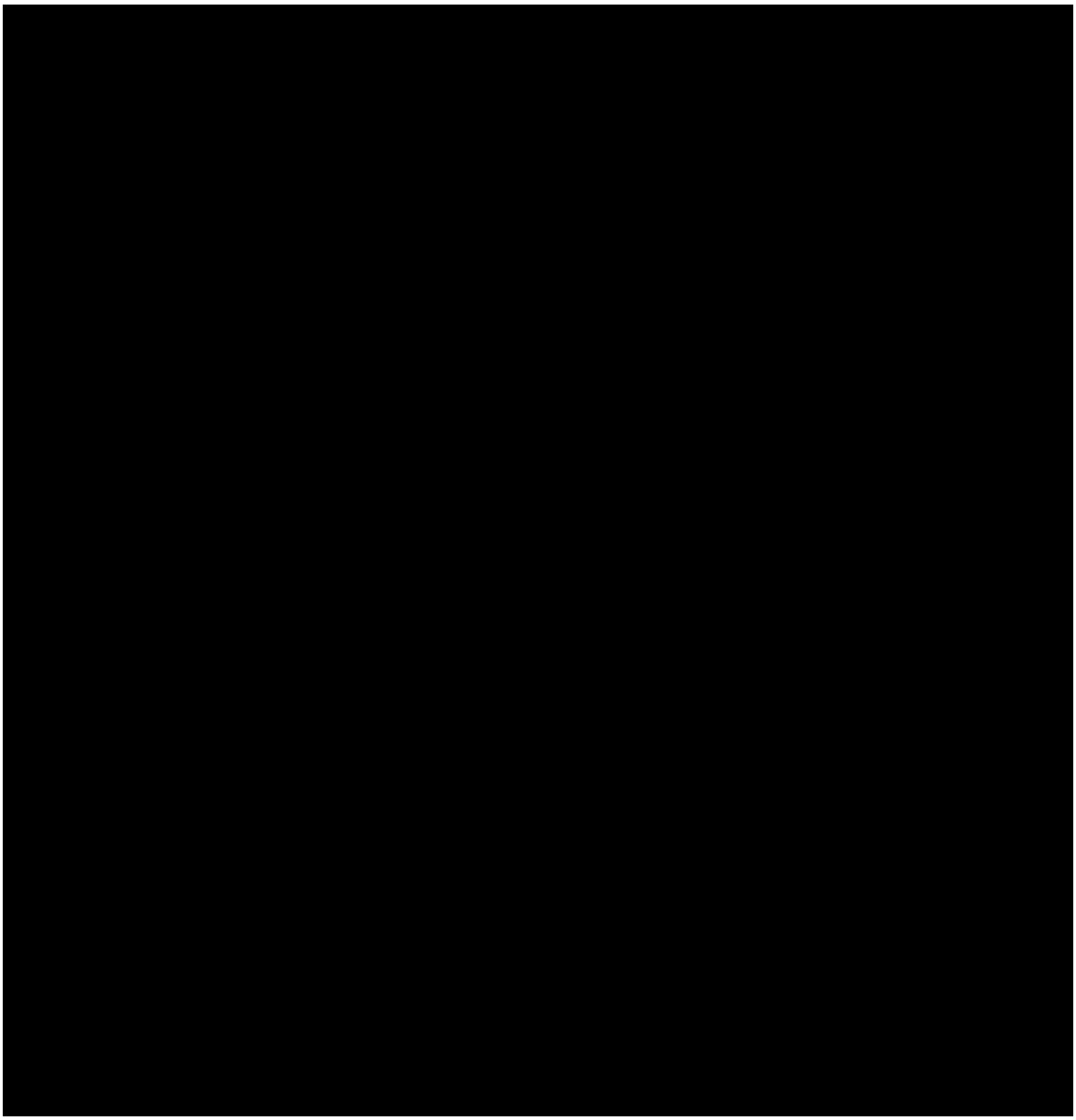
- Update table for monitoring and management of pituitary gland dysfunction to align with latest approved AMG 757 protocol
- Updated long-term follow-up language to continue radiographic imaging for subjects that discontinued treatment for any reason
- Updated language in dosage formulation and dosing instructions in Table 6-1 of investigational products
- Updated language in vital signs and pulse oximetry section to exclude supine positioning as a requirement for vital signs to be measured
- Updated language on recording and reporting of serious adverse events.
- Updated contraception and pregnancy language
- Added vaccine and COVID-19 language
- Included hypothyroidism, colitis, myasthenia gravis, and other additional risks as potential safety risk to AMG 404 based on recent available clinical data
- Administrative and editorial changes have been made throughout the protocol for clarification

Amendment 1

Protocol Title: A Phase 1b Study Evaluating the Safety and Efficacy of AMG 757 in Combination with AMG 404 in Subjects with Small Cell Lung Cancer (SCLC)

Amgen Protocol Number: AMG 757, AMG 404 20200439

Amendment Date: 26 July 2021



Approval Signatures

Document Name: Protocol Amendment tarlatamab 20200439 5

Document Description: 20200439 Protocol Amendment

Document Number: CLIN-000259408

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Type of Study Protocol: Amendment

Protocol Amendment No.: 5

Document Approvals	
Reason for Signing: Management	Name: [redacted] Date of Signature: 05-Jun-2024 23:30:10 GMT+0000
Reason for Signing: Management	Name: [redacted] Date of Signature: 06-Jun-2024 03:55:59 GMT+0000