Title Page

Protocol Title:		A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Subjects With Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy (DeLLphi-304)
Short Protocol Title:		Study Comparing Tarlatamab With Standard of Care Chemotherapy in Relapsed Small Cell Lung Cancer (DeLLphi-304)
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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 (International Council for Harmonisation [ICH] E6).

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I have read the attached protocol entitled A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Subjects With Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy (DeLLphi-304), dated **19 July 2024**, and agree to abide by all provisions set forth therein.

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_____
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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Subjects With Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy (DeLLphi-304)

Short Protocol Title: Study Comparing Tarlatamab With Standard of Care Chemotherapy in Relapsed Small Cell Lung Cancer (DeLLphi-304)

Study Phase: 3

Indication: Small cell lung cancer (SCLC)

Study Rationale

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). Due to its predominantly central location and propensity to metastasize early, it is seldom amenable to surgery. Although small cell lung cancer is exquisitely sensitive to first-line chemotherapy (approximately 60 to 70% response rates) and to radiation, most patients eventually die of recurrent disease. About 1 of 3 of SCLC patients present with limited stage (LS) disease, which is amenable to “curative-intent” treatment with combination chemo-radiation. Unfortunately, even in this setting, long-term remission is achieved in only 20% to 25%; the remainder relapsing with progressive disease (Elegbede et al, 2020).

Most patients with SCLC present with extensive stage (ES) disease. Extensive stage (ES) small cell lung cancer (SCLC) remains a grievous diagnosis with high unmet medical need. Despite initial high response rates to platinum-based first-line chemotherapy and immunotherapy, patients quickly develop resistance relapsing within 6 to 8 months. Response to second-line and subsequent therapies is limited, and patients die as a result of disease at a median time of 10 to 12 months from diagnosis (Rudin et al, 2015). Recent addition of **programmed cell death ligand 1 (**PD-**[**L**]**1**)** inhibitors to the **standard of care (**SOC**)** in ES disease has prolonged median overall survival (mOS) from 10 to about 12 months (Liu X et al, 2022) but 5-year survival in these patients remains extremely low at $< 3\%$ (Wang H et al, 2020).

Therapeutic options after first-line treatment for patients with progressive or recurrent small cell lung cancer are very limited. Progression on relapse is often rapid and

consequently, mOS after progression is a dismal 10 months. For those with a **chemotherapy-free interval (**CFI**)** of more than 6 months, a rechallenge with the original platin based doublet can be offered. For the majority with a shorter CFI or poorer performance status (PS), single agent topotecan is widely approved; however, it is associated with significant toxicity making it an unpopular choice. Lurbinectedin, a novel cytotoxic agent, offers a second option after receiving accelerated United States Food and Drug Administration (FDA) approval for this indication and has seen significant uptake in the US, and recently in other countries as well. Several other drugs such as irinotecan, paclitaxel, or combination regimens such as cyclophosphamide, adriamycin, and vincristine (CAV; all unapproved in this setting) are often used. This echoes the limited efficacy and high toxicity seen when treating the second line SCLC patient population reflecting a broad dissatisfaction with current options. Clearly, with limited second-line options and no approved therapy in the third-line setting, relapsed small cell lung cancer represents an acute area of unmet clinical need for most small cell lung cancer patients.

Delta-like ligand 3 (DLL3) is a non-canonical Notch ligand found intra-cellularly (localized in the Golgi apparatus) in normal tissues (Geffers et al, 2007). Delta-like ligand 3 is upregulated and aberrantly expressed on the cell surface in most SCLC tumors, making it a compelling target for T cell-based therapies (Saunders et al, 2015). In a diverse panel of normal tissues, a low level of staining with a cytoplasmic pattern was only detected in the brain, pituitary, and pancreatic islets (Study 123377), suggesting the potential for a DLL3-targeting therapy to be tumor specific in SCLC.

Tarlatamab (International Nonproprietary Name [INN]; AMG 757) is a novel half-life extended (HLE) bispecific T cell engager (BiTE®) molecule designed to direct T effector cells toward DLL3-expressing cells, with a tandem single chain fragment crystallizable (scFc) moiety for extended half-life. The pharmacological effect of tarlatamab is mediated by specific redirection of previously primed cytotoxic cluster of differentiation **(**CD**)** 3-positive T lymphocytes to kill DLL3-expressing cells.

Tarlatamab has demonstrated durable antitumor activity in subjects with ES-SCLC in a phase 2 (Study 20200491) and phase 1 study (Study 20160323) with a favorable benefit/risk profile. Please refer to the Investigator's Brochure for the most current efficacy and safety data across the tarlatamab program.

The aim of Study 20210004 is to evaluate the efficacy and safety of tarlatamab compared with SOC in subjects with relapsed SCLC who have progressed following

1 platinum-based regimen. The study consists of a 21-day screening period, a treatment period when subjects will be randomized to receive tarlatamab or SOC therapy (lurbinectedin or topotecan in US, Canada, Australia, Singapore, Korea; amrubicin in Japan; topotecan in all countries except Japan), a **safety follow-up (**SFU**)** visit, and an LTFU period.

Benefit/Risk Assessment

Delta-like ligand 3 is a promising target for the development of a T cell directed therapy due to the difference in expression levels between SCLC cells and normal tissues and the localization of DLL3 in the cytoplasm and cell membranes in tumor cells compared to localization that is restricted to the cytoplasm in normal tissues. Tarlatamab showed high activity in recruiting T cells against DLL3-expressing SCLC cell lines in vitro and significantly inhibited tumor growth in systemically treated tumor-bearing mice. Tarlatamab has demonstrated durable antitumor activity in subjects with ES-SCLC in a phase 2 (Study 20200491) and phase 1 study (Study 20160323) with a favorable benefit/risk profile. Please refer to the Investigator's Brochure for the most current efficacy and safety data across the tarlatamab program.

Based on experience with tarlatamab in ongoing clinical studies, the key safety information for tarlatamab includes the adverse drug reactions of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and neutropenia. Pituitary dysfunction, other neurologic events, and tumor lysis syndrome (TLS) are additional potential safety concerns of tarlatamab and are based on the biological mechanism of action, experience with other BiTE® molecules, and/or the potential for on-target, off-tumor effect. Please refer to the Investigator's Brochure for complete information.

Refer to Section 6.2.2 and Table 6-2 for detailed management recommendation.

Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the efficacy of tarlatamab with standard of care (SOC) on prolonging overall survival (OS)	• OS, defined as time from randomization until death from any cause
Attributes	**Primary Estimand**
• Target Population	• Subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy
• Primary Endpoint	• OS
• Summary Measures	• Hazard ratio (HR)
• Intercurrent Events and Strategies	• Start of new anti-cancer therapy OS will be estimated regardless of subsequent anti-cancer therapy (treatment policy strategy)
Primary Estimand Description	
• HR of OS between tarlatamab and SOC, for subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy, regardless of subsequent anti-cancer therapy (treatment policy strategy).	
Key Secondary - PFS	
• Compare the efficacy of tarlatamab with SOC as assessed by progression free survival (PFS) based on investigator assessment per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)	• PFS, defined as time from randomization until disease progression or death from any cause, whichever occurs first for all subjects. Progression will be based on investigator assessment of disease response per RECIST 1.1
Attributes	**Key Secondary Estimand: PFS**
• Target Population	• Subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy
• Key Secondary Endpoint	• PFS
• Summary Measures	• HR
• Intercurrent Events and Strategies	• Start of new anti-cancer therapy PFS will be censored at the last evaluable post-baseline tumor assessment prior to start of new anti-cancer therapy (hypothetical strategy)
Key Secondary Estimand Description - PFS	
• HR of PFS between tarlatamab and SOC, for subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy, prior to start of new anti-cancer therapy (hypothetical strategy)	

Key Secondary - PRO	
• Compare the treatment effect of tarlatamab with SOC on Patient-reported disease-related symptoms, Physical Function, and Quality of Life	• Change from Baseline assessed 6-weekly over time to 18 weeks Chest Pain as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC-QLQ-LC13) Cough as measured by EORTC-QLQ-LC13 Dyspnea as measured by EORTC Cancer Quality of Life Questionnaire 30 (EORTC-QLQ-C30) and EORTC-QLQ-LC13 Physical Function as measured by EORTC-QLQ-C30 Global Health Status of life as measured by EORTC-QLQ-C30
Attributes	**Key Secondary Estimand: PRO**
• Target Population	• Subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy
• Key Secondary Endpoint	• Patient-reported outcome (PRO)
• Summary Measures	• Change from Baseline assessed 6-weekly over time to 18 weeks
• Intercurrent Events and Strategies	• Discontinuation of treatment • PRO measurements before or on discontinuation of treatment will be used to estimate treatment effect (hypothetical strategy)
Key Secondary Estimand Description – PRO	
• Change from Baseline assessed 6-weekly over time to 18 weeks in PRO endpoints between tarlatamab and SOC, for subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy. PRO measurements before or on discontinuation of treatment will be used to estimate treatment effect (hypothetical strategy)	
Secondary	
• Compare the efficacy of tarlatamab with SOC as assessed by PFS at 1 year from randomization, objective response (OR), disease control (DC), and duration of response (DOR) based on investigator assessment per RECIST 1.1, and OS at 1 year, 2 years, and 3 years from randomization	• OR, defined as best overall response (BOR) of complete response (CR) + partial response (PR) • DC, defined as CR + PR + stable disease (SD) • DOR, defined as the time from the first documentation of OR until the first documentation of disease progression or death due to any cause, whichever occurs first. Only subjects who have achieved OR will be evaluated for DOR • PFS rate at 1 year from randomization

	• OS rate at 1 year, 2 years, and 3 years from randomization
• Compare the safety and tolerability of tarlatamab with SOC	• Incidence of treatment-emergent adverse events including grade ≥ 3 treatment-emergent adverse events, serious treatment-emergent adverse events, treatment-emergent adverse events leading to treatment discontinuation, fatal treatment-emergent adverse events, and treatment-related adverse events
• Characterize the pharmacokinetics (PK) of tarlatamab	• Serum concentrations of tarlatamab
• Evaluate the immunogenicity of tarlatamab	• Incidence of anti-tarlatamab antibody formation
• Compare the treatment effect of tarlatamab with SOC on remaining PRO measures	• Time to deterioration (TTD) for symptom scales Chest Pain as measured by EORTC-QLQ-LC13 Cough as measured by EORTC-QLQ-LC13 Dyspnea as measured by EORTC-QLQ-C30 and EORTC-QLQ-LC13 • Change from Baseline assessed 6-weekly over time to 18 weeks Pain as measured by Brief Pain Inventory - Short Form (BPI-SF) Remaining domains for QLQ-C30 and QLQ-LC13 Patient Global Impression of Severity (PGIS) (overall and for each symptom included in key secondary) Patient Global Impression of Change (PGIC) (overall and for each symptom included in key secondary) • Summary scores at each assessment and change from baseline of visual analogue scale (VAS) score as measured by 5-level EuroQol-5 Dimension (EQ5D-5L)
• Evaluate the severity and impact of symptomatic toxicity of tarlatamab and SOC	• Comparison of responses to selected questions from the PRO-CTCAE item bank • A single question from FACT-G on symptom bother

Overall Design

This is an open-label, randomized, multi-center, phase 3 study that will evaluate efficacy and safety of tarlatamab (AMG 757) compared with SOC therapy for the treatment of subjects with small cell lung cancer (SCLC) who have progressed after 1 prior line of platinum-containing therapy.

The study consists of a 21-day screening period, a treatment period, a safety follow-up visit, and a long-term follow-up (LTFU) period.

Subjects will be randomized with a 1:1 allocation ratio to receive tarlatamab or SOC therapy (lurbinectedin or topotecan in the US, Canada, Australia, Singapore, Korea; amrubicin in Japan; topotecan in all countries except Japan).

Randomization will be stratified by:

- Prior anti-programmed cell death 1 (PD-1) or prior anti-PD-(L)1 exposure (yes vs no)
- Chemotherapy-free interval (≥ 180 days; < 180 to ≥ 90 days; < 90 days)
- Presence (previous or current) of brain metastases (yes or no)
- Standard of care (topotecan/amrubicin vs lurbinectedin)

Chemotherapy-free interval is defined as the number of days elapsed between the last dose of prior chemotherapy and the date of first suspicion of disease relapse or progression (clinical or radiological). For example, if a patient experiences seizure and a brain metastasis progression is detected 48-hours after the seizure occurred, the date of progression is the date of this first seizure episode. Additionally, global enrollment will be monitored in order to ensure the majority of subjects have prior anti-PD-(L)1 exposure. **For patients with no exposure to prior anti-PD-(L)1, the reason for nonuse will be collected.**

Subjects will receive study treatment until investigator-determined radiographic disease progression per RECIST 1.1, unacceptable toxicity, withdrawal of consent, death, or end of study as determined by the sponsor (whichever occurs first). Following documented radiographic progression, the subject may remain on study treatment provided certain criteria are met. Refer to Section 6.1.7 for more details.

Upon permanent discontinuation from study treatment for any reason, an SFU visit will be performed approximately **60** (+ 5) days after last dose of study treatment, regardless of subsequent anti-cancer therapy that has been initiated within that period.

After the SFU visit, subjects will be followed in LTFU for survival every 12 weeks (± 14 days) from the SFU visit (or last imaging visit, whichever is later) for up to 3 years

after the last subject is enrolled, or 1 year from the subject's last dose of study treatment, whichever is later. **Ad hoc vital status (survival status) collection may be required to support key study analysis.**

The median time of subject's participation in the study treatment period will be approximately 4 to 6 months with median study duration to be approximately 9 to 12 months. The total study duration is expected to be approximately 4 years from the first subject enrolled to the final analysis.

Number of Subjects

Approximately [redacted] subjects will be enrolled at approximately 240 sites globally.

Summary of Subject Eligibility Criteria

Male and female subjects (age ≥ 18 years [or legal adult age within country, whichever is older]) with histologically or cytologically confirmed relapsed SCLC who progressed following 1 platinum-based regimen.

Once consented to the study, subjects will undergo protocol-required screening assessments to confirm all eligibility requirements of the study have been met. Subjects must have measurable lesions as defined per RECIST 1.1 within the 21-day screening period and must have adequate organ function.

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

Treatments

- **Amgen Investigational Product:** Tarlatamab
- **Non-Amgen Investigational Product:** Standard of care chemotherapy (lurbinectedin [US, Canada, Australia, Singapore, and Korea], topotecan [all countries, except Japan], or amrubicin [Japan])
- **Noninvestigational Product:** In some regions, the investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) administered as support or escape medication for preventative, diagnostic, or therapeutic reasons, or as SOC for a given diagnosis, may be considered noninvestigational medicinal products

Study treatment will be administered as follows:

- Tarlatamab will be administered as a 60-minute intravenous (IV) infusion with a step dose (1 mg tarlatamab) on cycle 1 day 1 (C1D1) followed by 10 mg target dose on cycle 1 day 8 (C1D8) and C1D15, and every 2 weeks (Q2W) thereafter (ie, C2+ D1/D15 dosing) in a 28-day cycle.
    - Monitoring - cycle 1: Monitoring required for 6 to 8 hours post-infusion at C1D1 and C1D8.

- Cohabitant (caregiver) support for 24 hours post-infusion and the ability to stay within 1 hour of a hospital for 24 hours is required.
- Counseling the subject and caregiver on signs and symptoms of CRS and ICANS by a health care provider is required prior to discharge.
- Subjects return to site on cycle 1 day 2 and cycle 1 day 9 for vital signs and physical examination.
- At subsequent visits, additional monitoring may be required post-infusion. Refer to Section 6.1.1 (Table 6-1).

  - Pre- and post-infusion medication requirements:
    - Dexamethasone: 8 mg IV (or equivalent) will be administered within 1 hour prior to tarlatamab infusion on C1D1 and C1D8
    - IV hydration: 1 L normal saline over 2 to 4 hours following tarlatamab doses on C1D1 and C1D8

- Standard of care (21-day cycle): Standard of care will be administered as follows in a 21-day cycle.
  - Lurbinectedin (US, Canada, Australia, Singapore, and Korea) will be administered as 3.2 mg/m^2 IV on day 1 every 3 weeks
  - Topotecan (all countries, except Japan and China) will be administered as IV at 1.5 mg/m^2 or oral at 2.3 mg/m^2/day on days 1, 2, 3, 4, and 5 every 3 weeks
  - Topotecan (China mainland [China mainland in this clinical study shall be referred as “China”]) will be administered as IV at 1.2 mg/m^2 or other locally approved dose or oral at 2.3 mg/m^2/day on days 1, 2, 3, 4, and 5 every 3 weeks
  - Amrubicin (Japan) will be administered as 40 mg/m^2 IV on days 1 to 3 every 3 weeks

For full understanding of the treatment groups, see the Study Schema (Section 1.2).

Statistical Considerations

Approximately [redacted] subjects per arm, total of approximately [redacted] subjects will be enrolled.

The hypotheses of the primary efficacy endpoint overall survival (OS), key secondary efficacy endpoint progression free survival (PFS), and key secondary patient-reported outcome (PRO) endpoints will be tested. The OS endpoint will be tested with [redacted] overall type I error (alpha) of [redacted]. If OS is significant, the key secondary efficacy endpoints of PFS and selected PRO endpoints can be tested sequentially in this order.

If both hypotheses of OS and PFS are rejected, the next 3 endpoints of change from baseline over time to week [redacted] in 3 lung cancer symptoms including chest pain, cough, and dyspnea will be tested using Holm’s procedure. Hypotheses are rejected sequentially based on the smallest p-value.

If all 3 hypotheses listed above are rejected, the next 2 PRO endpoints will be tested using the Holm's procedure, including change from baseline over time to week [redacted] in physical functioning and global health status. Hypotheses are rejected sequentially based on the smallest p-value.

Overall Survival (OS):

A total of [redacted] OS events will provide [redacted]% power to demonstrate superiority at an alternative HR of [redacted] with log-rank test using [redacted] overall type I error of [redacted] in a group sequential design with [redacted] interim analysis and [redacted] primary OS analysis. Under exponential assumption, assuming that the SOC mOS is [redacted] months (Spigel et al, 2021), a HR of [redacted] reflects a [redacted]-month improvement in OS of the tarlatamab arm over SOC arm. The interim analysis is triggered at the time when [redacted]% ([redacted] OS events occur. The dropout rate is anticipated to be [redacted]% per year assuming an exponential distribution.

With an enrollment rate of [redacted] subjects per month and a [redacted]-month ramp-up period ([redacted] subjects per month for the first [redacted] months), it is estimated that the OS interim and primary analyses occur at approximately [redacted] and [redacted] months respectively.

Progression-free Survival (PFS):

The analyses of PFS will occur once OS endpoints can claim statistical significance and will only be tested once.

Analysis methods: The primary inferential comparisons of the OS primary endpoint between tarlatamab and SOC arms will be made using a stratified log-rank test controlling for the randomization stratification factors. The HR and its 95% confidence interval (CI) will be estimated using a Cox proportional hazards model stratified by the randomization stratification factors. Stratum that is too small may be collapsed in the stratified log-rank analysis. The distribution of OS, including the median and quartiles and their corresponding 95% CIs will be characterized using the Kaplan-Meier method. Overall survival rates for selected landmarks (eg, 1 year and 2 years) will be reported with the 95% CI.

Progression free survival will be analyzed using the same approach as OS. Progression-free survival rate at 1 year will be reported with the 95% CI.

The analysis of ORR will use the Cochran-Mantel-Haenszel chi-square test controlling for the randomization stratification factors. An estimate of the common odds ratio

(95% CI) will be provided as a measure of the relative treatment effect. Objective response rate will be calculated and the 95% CI will be estimated using the Clopper-Pearson Method.

The descriptive analysis of DOR will be provided using the same methods as OS.

The change from baseline over time to 18 weeks in symptoms of chest pain and cough as measured by a single question from European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC-QLQ-LC13) will be analyzed using generalized linear mixed model for repeated measures with cumulative logit link. The change from baseline over time to [redacted] weeks in symptoms of dyspnea will be measured by a multiple item dyspnea domain from EORTC Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and EORTC-QLQ-LC13 Symptom Scores. The change from baseline over time to [redacted] weeks in physical functioning and global health status as measured by QLQ-C30 Domain Scores will be analyzed using a mixed model for repeated measurement (MMRM). Missing data for the MMRM will be handled under the assumption of missing at random (MAR). Further details of secondary endpoint testing will be described in the statistical analysis plan (SAP).

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

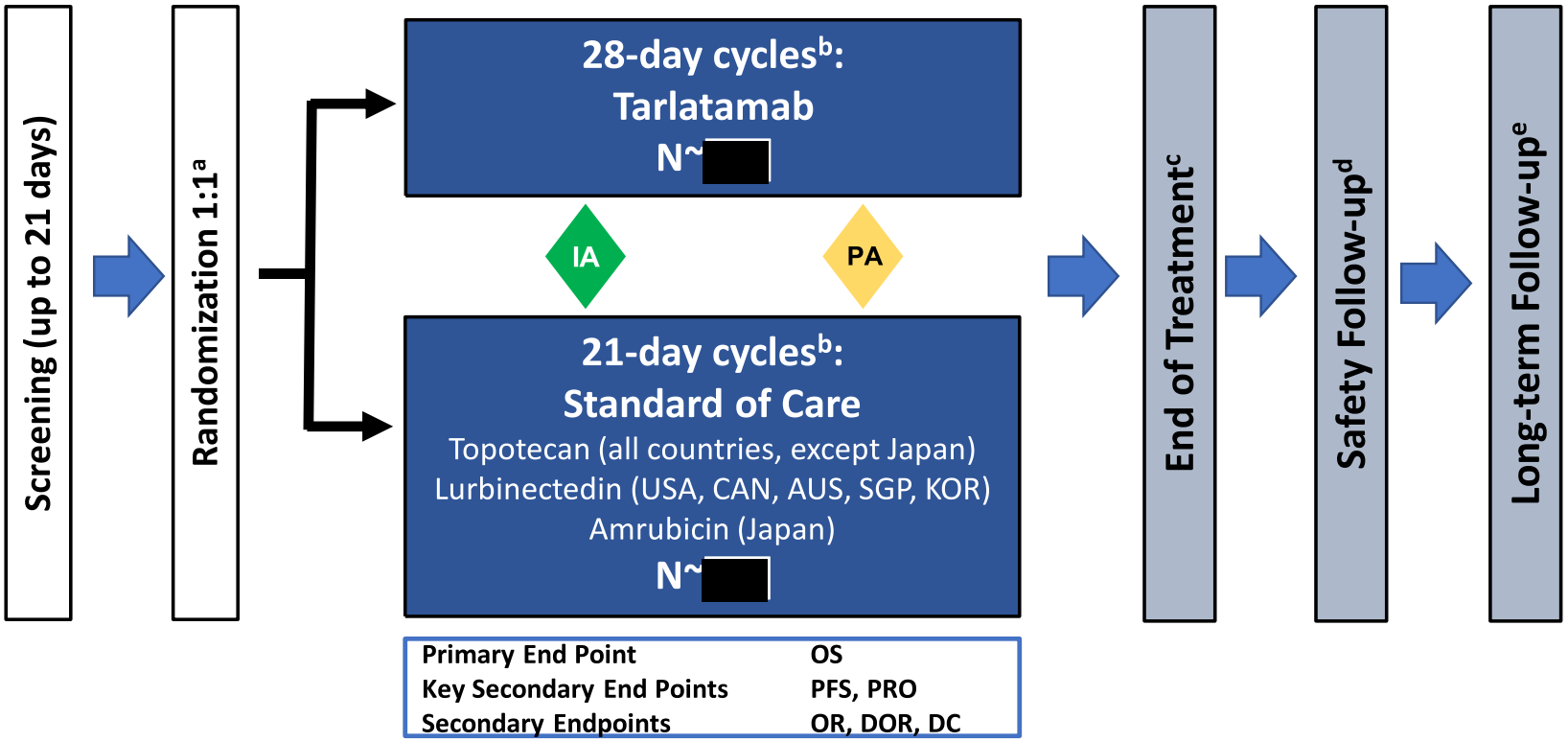
Statistical Hypotheses

The hypotheses of the primary efficacy endpoint and key secondary efficacy endpoints will be tested using the multiple testing procedure to control the study-level overall type I error rate below [redacted] levels, as discussed above.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



AUS = Australia; CAN = Canada; CFI = chemotherapy-free interval; DC = disease control; DOR = duration of response; IA = interim analysis; KOR = Korea; N = number of subjects; OR = objective response; OS = overall survival; PA = primary analysis; PD-L(1) = programmed cell death (ligand) 1; PFS = progression free survival; PRO = patient-reported outcomes; SFU = safety follow-up; SGP = Singapore; SOC =standard of care; USA = United States of America

[a] Stratified by: prior anti-PD-(L)1 exposure, CFI, presence (previous or current) of brain metastases (yes or no), and SOC.

[b] Subjects will receive study treatment until disease progression, unacceptable toxicity, withdrawal of consent, death, or end of study as determined by the sponsor (whichever occurs first).

[c] End of Treatment visit will occur at the time the decision is made to discontinue study treatment and prior to start of new anti-cancer treatment.

[d] Safety Follow-up visit will occur approximately **60** (+5) days after last study treatment administration.

[e] Long-term Follow-up for survival approximately every 12 weeks (± 14 days) after the SFU visit, or last imaging visit, whichever is later, for up to 3 years from last subject enrolled, or 1 year from the subject's last dose of study treatment, whichever is later.

1.3 Schedule of Activities (SoA)

Table 1-1. Tarlatamab Schedule of Activities – Cycle 1

Procedure[a]		Study Treatment							Notes
		Cycle 1[b]							
Week	SCR	1		2		3	4	As clinically indicated	
Day	-21 to 0	1	2	8	9	15	22		
GENERAL AND SAFETY ASSESSMENTS									
Informed consent	X								
Eligibility	X								**Eligibility criteria will be evaluated during screening and prior to randomization.**
Medical history	X								Includes medical/surgical and cancer history.
Demographics	X								
Substance use history	X								Substances: alcohol, tobacco
Randomization	X								Subjects must initiate the first administration of study treatment by end of the third calendar day from randomization. This will serve as C1D1. Randomization should be registered once all other screening assessments have been completed.
Physical examination	(X)	[X]	X	X	X	X		X	Physical exam must be completed prior to start of infusion on treatment days. (X): Height to be collected at screening only [X]: Must include weight at each day 1

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Footnotes defined on last page of this table.

Table 1-1. Tarlatamab Schedule of Activities – Cycle 1

Procedure[a]	SCR	Study Treatment						As clinically indicated	Notes
		Cycle 1[b]							
Week		1		2		3	4		
Day	-21 to 0	1	2	8	9	15	22		
GENERAL AND SAFETY ASSESSMENTS (CONT.)									
Neurological examination	X	X	X	X	X	X		X	Neurological exam must be completed prior to start of infusion on treatment days.
ECOG PS	X	X							
NYHA	X								**Collect** at screening **only** for **subjects with a known history of congestive heart failure to verify exclusion 207**
Vital signs, pulse oximetry	X	(X)	X	(X)	X	X		X	Includes systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature. (X): Vital signs will be assessed on C1D1 and C1D8 pre-infusion, end of infusion, and 60 (± 5) minutes after end of infusion.
12-lead ECG	X							X	12-lead ECG performed after subject rests for 5 minutes prior to recording. Single ECGs
ECHO or MUGA	X							X	

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Footnotes defined on last page of this table.

Table 1-1. Tarlatamab Schedule of Activities – Cycle 1

Procedure[a]	SCR	Study Treatment						As clinically indicated	Notes
		Cycle 1[b]							
Week		1		2		3	4		
Day	-21 to 0	1	2	8	9	15	22		
GENERAL AND SAFETY ASSESSMENTS (CONT.)									
Adverse events		continuous						X	Refer to Section 8.4.6.1.1.
Serious adverse events	continuous							X	Please refer to Section 8.4.6.1.2 and 8.4.6.1.3 for additional details.
Prior/Concomitant therapies review	continuous							X	Including, but not limited to, previous 3 months antibiotic therapy, and prior anti-cancer therapies for treatment of SCLC dating back to initial diagnosis.
LABORATORY ASSESSMENTS									
HIV, Hepatitis B and C	X							X	
Pregnancy test (females of childbearing potential only)[c]	X	X						X	Serum pregnancy test at screening within 7 days of C1D1; serum or urine pregnancy test on day 1 of every cycle and reviewed before treatment administration.

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Footnotes defined on last page of this table.

Table 1-1. Tarlatamab Schedule of Activities – Cycle 1

Procedure[a]	SCR	Study Treatment						As clinically indicated	Notes
		Cycle 1[b]							
Week		1		2		3	4		
Day	-21 to 0	1	2	8	9	15	22		
Hematology[d]	X	X		X		X		X	
Coagulation[d]	X	X		X		X		X	
Chemistry panel[d]	(X)	(X)		X		X		X	(X): Includes LDH and uric acid.
Lipase and amylase[e]	X	X						X	
Urinalysis[d]	X	X						X	
TSH and FT4[e]	X	X						X	
CENTRAL LABORATORY ASSESSMENTS									
Tumor tissue	X								**A**n archival tumor tissue block or slides **will be** collected prior to C1D1 (mandatory if such samples are available).
PK samples		X[a]							Collect up to 2 hours prior to start of tarlatamab infusion, and within 30 minutes after EOI.
Anti-tarlatamab antibody		X[a]				X[a]			Samples testing positive for binding antibodies will also be tested for neutralizing antibodies.

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Footnotes defined on last page of this table.

Table 1-1. Tarlatamab Schedule of Activities – Cycle 1

Procedure[a]	SCR	Study Treatment						As clinically indicated	Notes
		Cycle 1[b]							
Week		1		2		3	4		
Day	-21 to 0	1	2	8	9	15	22		
[redacted]									
IMAGING ASSESSMENTS									
MRI brain	X							X	All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. After screening, MRI of the brain can be performed at any time if clinically indicated (if subject has signs or symptoms suggestive of CNS metastases) per SOC.
Radiological imaging and tumor assessment	X								Must include chest, abdomen, pelvis, and all other known sites of disease. The same contrast and modality used at screening should be used for all subsequent assessments.

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Footnotes defined on last page of this table.

Table 1-1. Tarlatamab Schedule of Activities – Cycle 1

Procedure[a]	SCR	Study Treatment						As clinically indicated	Notes
		Cycle 1[b]							
Week		1		2		3	4		
Day	-21 to 0	1	2	8	9	15	22		
PATIENT-REPORTED OUTCOMES AND HEALTH ECONOMIC ASSESSMENTS									
EORTC-QLQ-C30	X	X		X		X	X		Must be completed before study specific procedures and before subject is informed of their disease status. PROs are to be collected regardless of dosing delay.
EORTC-QLQ-LC13	X	X							
PRO-CTCAE	X	X		X		X	X		
GP5 From FACT-G	X	X		X		X	X		
EQ5D-5L	X	X							
PGIS	X	X							
PGIC		X							
BPI-SF (Pain)	X	X							
STUDY TREATMENTS AND MONITORING									
Dexamethasone		X		X					Dexamethasone 8 mg IV (or equivalent) will be administered within 1 hour prior to tarlatamab infusion.
Tarlatamab Infusion		X		X		X			
IV hydration		X		X					IV hydration consisting of 1 L normal saline over 2 to 4 hours following completion of tarlatamab administration.

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Footnotes defined on last page of this table.

Table 1-1. Tarlatamab Schedule of Activities – Cycle 1

Procedure[a]	SCR	Study Treatment						As clinically indicated	Notes
		Cycle 1[b]							
Week		1		2		3	4		
Day	-21 to 0	1	2	8	9	15	22		
STUDY TREATMENTS AND MONITORING (CONT.)									
Monitoring		X		X					Subject will remain at study site for 6 to 8 hours post-infusion at C1D1 and C1D8. Cohabitant (caregiver) support for 24 hours post-infusion and the ability to stay within 1 hour of a hospital for 24 hours is required. Counseling the subject and caregiver on signs and symptoms of CRS and ICANS by a health care provider is required prior to discharge. Subjects return to site on C1D2 and C1D9 for vital signs and physical examination. At subsequent visits, extended monitoring may be required. Refer to Table 6-1.

BPI-SF = Brief Pain Inventory - Short Form; C1D1 = cycle 1 day 1; C1D2 = cycle 1 day 2; C1D8 = cycle 1 day 8; C1D9 = cycle 1 day 9; CRS = cytokine release syndrome; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CNS = central nervous system; [redacted]; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EORTC-QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ5D-5L = 5-level EuroQol - 5-Dimension; [redacted]; FACT-G = Functional Assessment of Cancer Therapy – General; FFPE = formalin-fixed, paraffin-embedded; FSH = follicle-stimulating hormone; FT4 = free T4; HIV = human immunodeficiency virus; ICANS = immune effector cell-associated neurotoxicity syndrome; IEC = independent ethics committee; IGF-1 = insulin like growth factor 1; IHC = immunohistochemistry; IRB = institutional review board; IV = intravenous; LDH = lactate dehydrogenase; LH = luteinizing hormone; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NYHA = New York Heart Association; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; SCLC = small cell lung cancer; SCR = screening; SFU = safety follow-up; SoA = schedule of activities; SOC = standard of care; TSH = thyroid-stimulating hormone.

[a] All procedures and assessments on dosing days are to be completed prior to study drug administration unless otherwise noted in the SoA.

[b] On-study cycle 1 visits may be completed within ± 1 day.

[c] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[d] If screening local labs are obtained within 48 hours prior to C1D1 dose, pre-infusion C1D1 samples do not have to be repeated. Where applicable, C1 D8 and D15 local labs may be obtained within 48 hours◦prior to dose (D8 and D15). Results must be reviewed prior to study drug administration.

[e] TSH and FT4, lipase and amylase if obtained within 72 hours prior to C1D1 dose, pre-infusion C1D1 samples do not have to be repeated. At subsequent visits, labs may be obtained up to 72 hours◦prior to dose. Results must be reviewed prior to study drug administration.

Table 1-2. Tarlatamab Schedule of Activities – Cycle 2+

	Study Treatment[b]									As clinically indicated	EOT	SFU[c]	LTFU[d]	Notes
Procedure[a]	**Cycle 2**				**Cycle 3+**				**Q6W[h]**					
Week	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**						
Day	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**						
GENERAL AND SAFETY ASSESSMENTS														
Physical examination	(X)		X		(X)		X			X	X	X		Physical exam must be completed prior to start of infusion on treatment days. (X): Must include weight at each day 1
Neurological examination	X		X		X		X			X	X	X		Neurological exam must be completed prior to start of infusion on treatment days.
ECOG PS	X				X						X	X		
Vital signs, pulse oximetry	X		X		X		X			X	X	X		
12-lead ECG										X	X			Single ECGs
ECHO or MUGA										X				
Vital status (survival status**)**											**X**	**X**	X	
Subsequent anti-cancer therapy											X	X	X	
Adverse events	continuous													Refer to Section 8.4.6.1.1.
Serious adverse events	continuous												X	**During the LTFU phase, serious adverse events suspected to be related to investigational product will be reported to Amgen.** **After end of study, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen.** Please refer to Section 8.4.6.1.2 and 8.4.6.1.3 for additional details.
Prior/Concomitant therapies review	continuous													

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Table 1-2. Tarlatamab Schedule of Activities – Cycle 2+

Procedure[a]	Study Treatment[b]									As clinically indicated	EOT	SFU[c]	LTFU[d]	Notes
	Cycle 2				Cycle 3+				Q6W[h]					
Week	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**						
Day	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**						
LABORATORY ASSESSMENTS														
HIV, Hepatitis B and C										X				
Pregnancy test (females of childbearing potential only)[e]	X				X					X	(X)	**(X)**		Serum or urine pregnancy test on day 1 of every cycle should be collected and reviewed before treatment administration. (X): Additional pregnancy test required **60** days after the last dose of tarlatamab
Hematology[f]	X		X		X		(X)			X	X	X		(X): cycle 3, 4, and 5 only
Coagulation[f]	X		X		X					X	X	X		
Chemistry panel[f]	**[X]**		X		X		(X)			X	X	X		**[X]:** Includes LDH and uric acid on C2D1. (X): cycle 3, 4, and 5 only
Lipase and amylase[g]	X				X					X	X	X		
Urinalysis[f]					(X)					X	X	X		(X): cycle 3 and every 2 cycles thereafter (eg, C5, C7, C9, etc,)
TSH and FT4[g]											X			
CENTRAL LABORATORY ASSESSMENTS														
Tumor tissue											(X)			(X): Optional Tumor tissue sample may be collected in the event of tumor progression.
PK samples	X[a]				X[a,i]									Collect up to 2 hours prior to start of tarlatamab infusion, and within 30 minutes after EOI **in cycle 2 and cycle 3. See footnote i for instructions for cycle 4 and beyond.** The time of dosing and PK sample collection should be accurately recorded.
Anti-tarlatamab antibody	X[a]				**(X)**[a]						X[a]	X[a]		**(X):** Collect **at C3D1, C4D1 and then every other cycle (eg C6D1, C8D1, etc until SFU)** [a]. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies.

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Table 1-2. Tarlatamab Schedule of Activities – Cycle 2+

Procedure[a]	Study Treatment[b]									As clinically indicated	EOT	SFU[c]	LTFU[d]	Notes
	Cycle 2				Cycle 3+				Q6W[h]					
Week	1	2	3	4	1	2	3	4						
Day	1	8	15	22	1	8	15	22						
[redacted]														

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Table 1-2. Tarlatamab Schedule of Activities – Cycle 2+

Procedure[a]	Study Treatment[b]									As clinically indicated	EOT	SFU[c]	LTFU[d]	Notes
	Cycle 2				Cycle 3+				Q6W[h]					
Week	1	2	3	4	1	2	3	4						
Day	1	8	15	22	1	8	15	22						
IMAGING ASSESSMENTS														
MRI brain imaging and tumor assessment										X				All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. After screening, MRI of the brain can be performed at any time if clinically indicated (if subject has signs or symptoms suggestive of CNS metastases) per SOC.
Radiological imaging and tumor assessment									X	X	(X)	(X)	[X]	Weeks 1 to 48: Q6W (± **7** days) Weeks 49+: Q12W (± **7** days) Must include chest, abdomen, pelvis, and all other known sites of disease (including brain). The same contrast and modality used at screening should be used for all subsequent assessments. Confirmation of response is required. (X): Required at the EOT or SFU visit **(± 7 days)** if the subject has not had radiologic imaging performed within 6 weeks of the visit (if ending treatment on or before week 48) or within 12 weeks of the visit (if ending treatment after week 48). [X]: For subjects who end study treatment for reasons other than radiographic PD, full withdrawal of consent, death, or loss to follow up, every effort should be made to perform radiologic imaging (CT/MRI) until radiographic progression. Subjects who are eligible to remain on study treatment after first disease progression must complete all protocol-required procedures as noted in the SoA, including radiologic imaging. Refer to Section 8.3.1 for additional details.

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Table 1-2. Tarlatamab Schedule of Activities – Cycle 2+

Procedure[a]	Study Treatment[b]									As clinically indicated	EOT	SFU[c]	LTFU[d]	Notes
	Cycle 2				Cycle 3+				Q6W[h]					
Week	1	2	3	4	1	2	3	4						
Day	1	8	15	22	1	8	15	22						
PATIENT-REPORTED OUTCOMES AND HEALTH ECONOMIC ASSESSMENTS														
EORTC-QLQ-C30	X	X	X	X	(X)	(X)	(X)	(X)	[X]		X	X		Must be completed before study specific procedures and before subject is informed of their disease status. PROs are to be collected regardless of dosing delay. Cycles 3+ **Q6W: (± 7 days)** (X): Collect at cycle 3 only. [X]: Collect on cycle 4 day 1 and every 6 weeks thereafter.
EORTC-QLQ-LC13			X						[X]		X	X		
PRO-CTCAE	X	X	X	X	(X)	(X)	(X)	(X)	[X]		X	X		
GP5 From FACT-G	X	X	X	X	(X)	(X)	(X)	(X)	[X]		X	X		
EQ5D-5L			X						[X]		X	X		
PGIS			X						[X]		X	X		
PGIC			X						[X]		X	X		
BPI-SF (Pain)			X						[X]		X	X		
STUDY TREATMENTS AND MONITORING														
Dexamethasone										(X)				(X): Dexamethasone 8 mg IV (or equivalent) will be administered within 1 hour prior to tarlatamab infusion.
Tarlatamab Infusion	X		X		X		X							
Monitoring										X				Additional monitoring may be recommended post-infusion based on occurrence of CRS, ICANS, or ICANS-related neurological events. Refer to Table 6-1.

BPI-SF = Brief Pain Inventory - Short Form; C1D1 = cycle 1 day 1; C1D8 = cycle 1 day 8; C2D1 = cycle 2 day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; [redacted] ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOT = end of treatment; EORTC-QLQ = European Organization for Research and Treatment of Cancer Quality of life Questionnaire; EQ5D-5L = 5-level EuroQol - 5-Dimension; [redacted]; FACT-G = Functional Assessment of Cancer Therapy – General; FSH = follicle-stimulating hormone; FT4 = free T4; HIV = human immunodeficiency virus; ICANS - immune effector cell-associated neurotoxicity syndrome; IGF-1 = insulin like growth factor 1; LDH = lactate dehydrogenase; LH = luteinizing hormone; LSE = last subject enrolled; LTFU = long-term follow-up; MRI = magnetic resonance imaging; MUGA scan = multigated acquisition scan; PD = progressive disease; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; Q6W = every 6 weeks; SCLC = small cell lung cancer; SFU = safety follow-up; SoA = schedule of activities; SOC = standard of care; TSH = thyroid-stimulating hormone.

[a] All procedures and assessments on dosing days are to be completed prior to study drug administration unless otherwise noted in the SoA.

[b] On-study cycle 2 visits have a ± 2-day window and all subsequent visits beginning in cycle 3 will have a ± 3-day window, unless otherwise specified.

[c] Safety Follow-up visit will occur approximately **60** (+ 5) days after last dose of study treatment.

[d] Long-term Follow-up will occur every 12 weeks (± 14 days) from the SFU visit or last imaging visit, whichever is later for up to 3 years after LSE, or 1 year from the subject's last dose of study treatment, whichever is later. **Ad hoc vital status (survival status) collection may be required to support key study analysis.**

[e] **Highly sensitive serum pregnancy test (for subjects of childbearing potential) at screening; serum or urine pregnancy test on day 1 of every cycle while receiving investigational product and then monthly following EOT until 60 days from the last tarlatamab dose.** Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[f] Local labs may be obtained within 48 hours prior to dose. Results must be reviewed prior to study drug administration.

[g] TSH and FT4, lipase and amylase if obtained within 72 hours prior to dose. Results must be reviewed prior to study drug administration.

[h] Q6W (every 6 weeks **[± 7 days]**) from C1D1; except where noted in the SoA for [redacted]

[i] **Starting in cycle 4, collect predose PK samples only (up to 2 hours prior to start of infusion) every other cycle through Cycle 12 (C4, C6, C8, C10, C12).**

Table 1-3. Standard of Care Schedule of Activities

Procedure[a]	SCR	Study Treatment (21-day [+3 day] Cycles)							Q6W[g]	As Clinically Indicated	EOT	SFU[b]	LTFU[c]	NOTES
Day	-21 to 0	1	2	3	4	5	8	15						
GENERAL AND SAFETY ASSESSMENTS														
Informed consent	X													
Eligibility	X													**Eligibility criteria will be evaluated during screening and prior to randomization.**
Medical History	X													Includes medical/surgical and cancer history.
Demographics	X													
Substance use history	X													Substances: alcohol, tobacco
Randomization	X													Subjects must initiate the first administration of study treatment by end of the third calendar day from randomization. This will serve as C1D1. Randomization should be registered once all other screening assessments have been completed.
Physical examination	(X)	[X]								X	X	X		Physical exam must be completed prior to dose administration on treatment days. (X): Height to be collected at screening only [X]: Must include weight and BSA BSA should be calculated during screening per Mosteller formula and utilized to calculate required study drug doses.
Neurological examination	X	X								X	X	X		Neurological exam must be completed prior to start of infusion on treatment days.
ECOG PS	X	X									X	X		
NYHA	X													**Collect** at screening **only** for **subjects with known history of congestive heart failure to verify exclusion 207**.
12-lead ECG	X									X	X			Single ECGs

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Table 1-3. Standard of Care Schedule of Activities

Procedure[a]	SCR	Study Treatment (21-day [+3 day] Cycles)							Q6W[g]	As Clinically Indicated	EOT	SFU[b]	LTFU[c]	NOTES
Day	-21 to 0	1	2	3	4	5	8	15						
GENERAL AND SAFETY ASSESSMENTS (CONT.)														
Vital signs, pulse oximetry	X	X	(X)	(X)	(X)	(X)				X	X	X		Includes systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature. (X): For subjects on topotecan IV (on days 2 to 5), and for subjects on amrubicin (on days 2 to 3). Refer to Section 8.4.1 for detailed vital sign collection time points.
ECHO or MUGA	X									X				
Vital status (survival status)											**X**	**X**	X	
Subsequent anti-cancer therapy											X	X	X	
Adverse events		continuous												Refer to Section 8.4.6.1.1.
Serious adverse events	continuous												X	**During the LTFU phase, serious adverse events suspected to be related to investigational product will be reported to Amgen.** **After end of study, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen.** Please refer to Section 8.4.6.1.2. and 8.4.6.1.3 for additional details.
Prior/Concomitant therapies review	continuous													Including, but not limited to, previous 3 months antibiotic therapy, and prior anti-cancer therapies for treatment of SCLC dating back to initial diagnosis.

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Table 1-3. Standard of Care Schedule of Activities

Procedure[a]	SCR	Study Treatment (21-day [+3 day] Cycles)							Q6W[g]	As Clinically Indicated	EOT	SFU[b]	LTFU[c]	NOTES
Day	-21 to 0	1	2	3	4	5	8	15						
LABORATORY ASSESSMENTS														
HIV, Hepatitis B and C	X									X				
Pregnancy test (females of childbearing potential only)[d]	X	X								X	X	(X)		Serum pregnancy test at screening within 7 days of C1D1; serum or urine pregnancy test on day 1 of every cycle and reviewed before treatment administration. (X): Additional pregnancy test for SOC therapies is based on regional prescribing information.
Hematology[e]	X	X								X	X	X		
Coagulation[e]	X	X								X	X	X		
Chemistry panel[e]	X	X								X	X	X		Includes LDH and uric acid in **Screening, C1D1,** and **C2D1 only.**
Lipase and amylase[f]	X	X								X	X	X		
Urinalysis[e]	X									X	X	X		
TSH and FT4[f]	X	X									X			Cycle 1 only
CENTRAL LABORATORY ASSESSMENTS														
Tumor Tissue	X										(X)			**A**n archival tumor tissue block or slides **will be** collected prior to C1D1 (mandatory if such samples are available). (X): Optional Tumor tissue sample may be collected in the event of tumor progression.

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Table 1-3. Standard of Care Schedule of Activities

Procedure[a]	SCR	Study Treatment (21-day [+3 day] Cycles)							Q6W[g]	As Clinically Indicated	EOT	SFU[b]	LTFU[c]	NOTES
Day	-21 to 0	1	2	3	4	5	8	15						
[redacted]														

Footnotes defined on last page of this table.

Table 1-3. Standard of Care Schedule of Activities

Procedure[a]	SCR	Study Treatment (21-day [+3 day] Cycles)							Q6W[g]	As Clinically Indicated	EOT	SFU[b]	LTFU[c]	NOTES
Day	-21 to 0	1	2	3	4	5	8	15						
IMAGING ASSESSMENTS														
MRI brain	X									X				All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. After screening, MRI of the brain can be performed at any time if clinically indicated (if subject has signs or symptoms suggestive of CNS metastases) per SOC.
Radiological imaging and tumor assessment	X								X	X	(X)	(X)	[X]	Weeks 1 to 48: Q6W (± **7** days) Weeks 49+: Q12W (±**7** days) Must include chest, abdomen, pelvis, and all other known sites of disease (including brain). The same contrast and modality used at screening should be used for all subsequent assessments. Confirmation of response is required. (X): Required at the EOT or SFU visit **(± 7 days)** if the subject has not had radiologic imaging performed within 6 weeks of the visit (if ending treatment on or before week 48) or within 12 weeks of the visit (if ending treatment after week 48). [X]: For subjects who end study treatment for reasons other than radiographic PD, full withdrawal of consent, death, or loss to follow up, every effort should be made to perform radiologic imaging (CT/MRI) until radiographic progression. Refer to Section 8.3.1 for additional details.

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Table 1-3. Standard of Care Schedule of Activities

Procedure[a]	SCR	Study Treatment (21-day [+3 day] Cycles)							Q6W[g]	As Clinically Indicated	EOT	SFU[b]	LTFU[c]	NOTES
Day	-21 to 0	1	2	3	4	5	8	15						
PATIENT-REPORTED OUTCOMES AND HEALTH ECONOMIC ASSESSMENTS														
EORTC-QLQ-C30	X	X					[X]	[X]	X		X	X		Completed before study specific procedures and before subject is informed of their disease status. PROs are to be collected regardless of dosing delay. **Q6W**: **(± 7 days)** (X): In addition to EORTC-QLQ-C30, PRO-CTCAE, and GP5 from FACT-G, collect all other PROs at cycle 1 day 1 and every 6 weeks thereafter. [X]: Collect weekly for first 12 weeks and then every 6 weeks thereafter.
EORTC-QLQ-LC13	X	(X)							X		X	X		
PRO-CTCAE	X	X					[X]	[X]	X		X	X		
GP5 From FACT-G	X	X					[X]	[X]	X		X	X		
EQ5D-5L	X	(X)							X		X	X		
PGIS	X	(X)							X		X	X		
PGIC		(X)							X		X	X		
BPI-SF (Pain)	X	(X)							X		X	X		
STUDY TREATMENTS														
Lurbinectedin administration		X												USA, Canada, Australia, Singapore, and Korea
Topotecan administration		X	X	X	X	X								All countries, except Japan. Additional dosing information will be collected through a web-based diary when subjects self-administer oral topotecan at home.
Amrubicin administration		X	X	X										Japan

BPI-SF = Brief Pain Inventory - Short Form; C1D1 = cycle 1 day 1; C1D8 = cycle 1 day 8; C4D1 = cycle 4 day 1; CR = complete response; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; [redacted]; D1 = day 1; EC = Ethics Committee; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC-QLQ = European Organization for Research and Treatment of Cancer Quality of life Questionnaire; EOT = end of treatment; EQ5D-5L = 5-level EuroQol – 5-Dimension; [redacted]; FACT-G = Functional Assessment of Cancer Therapy – General; FFPE = formalin-fixed, paraffin-embedded; FSH = follicle-stimulating hormone; FT4 = free T4; HIV = human immunodeficiency virus; IEC = independent ethics committee; IGF-1 = insulin like growth factor 1; IHC = immunohistochemistry; IRB = Institutional Review Board; IV = intravenous; LC13 = lung cancer 13; LDH = lactate dehydrogenase; LH = luteinizing hormone; LSE = last subject enrolled; LTFU = long-term follow-up; MRI = magnetic resonance imaging; MUGA scan = multigated acquisition scan; NYHA = New York Heart

Association; PD = progressive disease; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; PO = per oral; PR = partial response; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PROs = Patient Reported Outcomes; Q6W = every 6 weeks; SCLC = small cell lung cancer; SCR = screening; SFU = safety follow-up; SoA = schedule of activities; SOC = standard of care; TSH = thyroid-stimulating hormone; USA = United States of America.

[a] All procedures and assessments on dosing days are to be completed prior to study drug administration unless otherwise noted in the SoA.

[b] Safety Follow-up visit will occur approximately **60** (+5) days after last dose of study treatment.

[c] Long-term Follow-up will occur every 12 weeks (± 14 days) from the SFU visit or last imaging visit, whichever is later for up to 3 years after LSE, or 1 year from the subject's last dose of study treatment, whichever is later. **Ad hoc vital status (survival status) collection may be required to support key study analysis.**

[d] **Highly sensitive serum pregnancy test (for subjects of childbearing potential) at screening; serum or urine pregnancy test on day 1 of every cycle while receiving investigational product and then monthly following EOT until 60 days from the last tarlatamab dose.** Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[e] If screening local labs are obtained within 48 hours prior to C1D1 dose, pre-infusion C1D1 samples do not have to be repeated. **C**ycle 2 and beyond, local labs may be obtained within 48 hours prior to dose. Results must be reviewed prior to study drug administration.

[f] TSH and FT4, lipase and amylase if obtained within 72 hours prior to C1D1 dose, pre-infusion C1D1 samples do not have to be repeated. At subsequent visits, local labs may be obtained up to 72 hours prior to dose. Results must be reviewed prior to study drug administration.

[g] Q6W (every 6 weeks **[± 7 days]**) from C1D1; except where noted in the SoA for [redacted]

2. Introduction

2.1 Study Rationale

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). Due to its predominantly central location and propensity to metastasize early, it is seldom amenable to surgery. Although small cell lung cancer is exquisitely sensitive to first-line chemotherapy (approximately 60 to 70% response rates) and to radiation, most patients eventually die of recurrent disease. About 1 of 3 of SCLC patients present with LS disease, which is amenable to “curative-intent” treatment with combination chemo-radiation. Unfortunately, even in this setting, long-term remission is achieved in only 20% to 25%; the remainder relapsing with progressive disease (Elegbede et al, 2020).

The majority (2 of 3) of SCLC patients present with more advanced ES disease. Extensive stage (ES) SCLC (ES-SCLC) remains a grievous diagnosis with high unmet medical need. Despite initial response to chemotherapy, patients invariably experience disease progression and develop resistance to second-line and subsequent therapies. Response to second-line and subsequent therapies is limited, and patients die as a result of disease at a median time of 10 to 12 months from diagnosis (Rudin et al, 2015). Recent addition of PD-(L)1 inhibitors to the **standard of care (**SOC**)** in ES disease has prolonged mOS from 10 to about 12 months (Liu X et al, 2022) but 5-year survival in these patients remains extremely low at < 3% (Wang H et al, 2020).

Therapeutic options after first-line treatment for patients with progressive or recurrent small cell lung cancer are very limited. Progression on relapse is often rapid and consequently, mOS after progression is a dismal 10 months. For those with a CFI of more than 6 months, a rechallenge with the original platin based doublet can be offered. For the majority with a shorter CFI or poorer PS, single agent topotecan is widely approved; however, it is associated with significant toxicity making it an unpopular choice. Lurbinectedin, a novel cytotoxic agent, offers a second option after receiving accelerated FDA approval for this indication and has seen significant uptake in the US, and recently in other countries as well. Several other drugs such as irinotecan, paclitaxel, or combination regimens such as cyclophosphamide, adriamycin, and vincristine (CAV; all unapproved in this setting) are often used. This echoes the limited efficacy and high toxicity seen when treating the second line SCLC patient population reflecting a broad dissatisfaction with current options. Clearly, with limited second-line

options and no approved therapy in the third-line setting, relapsed small cell lung cancer represents an acute area of unmet clinical need for most small cell lung cancer patients.

Delta-like ligand 3 (DLL3) is a non-canonical Notch ligand found intra-cellularly (localized in the Golgi apparatus) in normal tissues (Geffers et al, 2007). Delta-like ligand 3 is upregulated and aberrantly expressed on the cell surface in most SCLC tumors, making it a compelling target for T cell-based therapies (Saunders et al, 2015). In a diverse panel of normal tissues, a low level of staining with a cytoplasmic pattern was only detected in the brain, pituitary, and pancreatic islets (Study 123377), suggesting the potential for a DLL3-targeting therapy to be tumor specific in SCLC.

Tarlatamab (International Nonproprietary Name [INN]; AMG 757) is a novel half-life extended (HLE) bispecific T cell engager (BiTE®) molecule designed to direct T effector cells toward DLL3-expressing cells, with a tandem scFc moiety for extended half-life. The pharmacological effect of tarlatamab is mediated by specific redirection of previously primed cytotoxic **cluster of differentiation (**CD**)**3^+ T lymphocytes to kill DLL3-expressing cells.

Tarlatamab has demonstrated durable antitumor activity in subjects with ES-SCLC in a phase 2 (Study 20200491) and phase 1 study (Study 20160323) with a favorable benefit/risk profile. Please refer to the Investigator's Brochure for the most current efficacy and safety data across the tarlatamab program.

The aim of Study 20210004 is to evaluate efficacy and safety of tarlatamab compared with SOC therapy in subjects with relapsed SCLC who have progressed following 1 platinum-based regimen. The study consists of a 21-day screening period, a treatment period when subjects will be randomized to receive tarlatamab or SOC therapy (lurbinectedin or topotecan in US, Canada, Australia, Singapore, Korea; amrubicin in Japan; topotecan in all countries except Japan), an SFU visit, and an LTFU period.

2.2 Background

2.2.1 Disease

Small cell lung cancer, 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 (LS), most cases have disease not encompassed

by 1 radiotherapy field (ES). Small cell lung cancer is exquisitely sensitive to first-line chemotherapy (approximately 60% to 70% response rates) and to radiation which is in stark contrast to resistance to second-line and subsequent therapies after disease recurrence (Byers and Rudin, 2015). Patients with ES-SCLC 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 SCLC, first-line treatment is platinum-based chemotherapy. Most patients in the US receive platinum-etoposide (EP) chemotherapy (with either carboplatin or cisplatin), and some patients receive platinum-irinotecan as an alternative, especially outside the US. With limited second-line options and no approved therapy in the third-line setting, relapsed SCLC represents an area of acute unmet need.

2.2.2 Amgen Investigational Product Background: Tarlatamab

BiTE® molecules have been designed to direct T effector memory cells towards target cells. The proximity induced by the BiTE® triggers target cell specific cytotoxicity which closely resembles standard cytotoxic T lymphocyte activation.

Tarlatamab is an HLE BiTE® molecule combining the binding specificities for DLL3 and CD3 genetically fused to the N-terminus of immunoglobulin G (IgG) scFv region and is being developed with the intent to treat patients with SCLC. The anti-tumor 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 $CD3^+$ T lymphocytes to kill $DLL3^+$ cells.

The pivotal phase 2 study of tarlatamab in patients with relapsed SCLC after 2 lines of prior therapy has confirmed durable efficacy and favorable benefit/risk profile (Study 20200491). Based on a pre-specified interim analysis (IA) in part 1 of the phase 2 Study 20200491 the regimen using 10 mg target dose with a 1 mg step-dose was selected as the monotherapy recommended phase 2 dose (RP2D) regimen to balance the efficacy/safety of tarlatamab and to be further evaluated in part 2 and part 3 of the phase 2 Study 20200491, and any subsequent studies for tarlatamab. The primary analysis for the phase 2 Study 20200491 reinforced the selection of 10 mg target dose for tarlatamab studies.

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

2.3 Benefit/Risk Assessment

Delta-like ligand 3 is a promising target for the development of a T cell-directed therapy due to the difference in expression levels between SCLC cells and normal tissues and the localization of DLL3 in the cytoplasm and cell membranes in tumor cells compared to localization that is restricted to the cytoplasm in normal tissues. Tarlatamab showed high activity in recruiting T cells against DLL3-expressing SCLC cell lines in vitro and significantly inhibited tumor growth in systemically treated tumor-bearing mice. Tarlatamab has demonstrated durable antitumor activity in subjects with ES-SCLC in a phase 2 (Study 20200491) and phase 1 study (Study 20160323) with a favorable benefit/risk profile. Please refer to the Investigator's Brochure for the most current efficacy and safety data across the tarlatamab program.

Key Safety Information

Based on experience with tarlatamab in ongoing clinical studies, the key safety information for tarlatamab includes the adverse drug reactions of cytokine release syndrome (CRS), immune effector cell associated neurotoxicity syndrome (ICANS), and neutropenia. Pituitary dysfunction, other neurologic events, and tumor lysis syndrome (TLS) are additional potential safety concerns of tarlatamab and are based on the biological mechanism of action, experience with other BiTE molecules, and/or the potential for on-target, off-tumor effect. Please refer to the Investigator's Brochure for complete information.

Refer to Section 6.2.2 and Table 6-2 for detailed management recommendation.

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

Amgen closely monitors the coronavirus disease 2019 (COVID-19) pandemic around the world. As part of this effort, Amgen performs a rigorous assessment, considering the study design, patient safety, public health risk, benefit-risk assessment, as well as the burden on country healthcare systems. Decisions are made on a study-by-study and country-by-country basis to minimize risk to patients and avoid undue burden on healthcare facilities.

The above benefit risk assessment supports the conduct of this clinical trial. Refer to the Investigator's Brochure for additional information related to risk assessment.

3. Objective(s) and Endpoint(s)

Objectives	**Endpoints**
Primary	
• To compare the efficacy of tarlatamab with standard of care (SOC) on prolonging overall survival (OS)	• OS, defined as time from randomization until death from any cause
Attributes	**Primary Estimand**
• Target Population	• Subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy
• Primary Endpoint	• OS
• Summary Measures	• Hazard ratio (HR)
• Intercurrent Events and Strategies	• Start of new anti-cancer therapy OS will be estimated regardless of subsequent anti-cancer therapy (treatment policy strategy)
Primary Estimand Description	
• HR of OS between tarlatamab and SOC, for subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy, regardless of subsequent anti-cancer therapy (treatment policy strategy).	
Key Secondary - PFS	
• Compare the efficacy of tarlatamab with SOC as assessed by progression free survival (PFS) based on investigator assessment per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)	• PFS, defined as time from randomization until disease progression or death from any cause, whichever occurs first for all subjects. Progression will be based on investigator assessment of disease response per RECIST 1.1
Attributes	**Key Secondary Estimand: PFS**
• Target Population	• Subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy
• Key Secondary Endpoint	• PFS
• Summary Measures	• HR
• Intercurrent Events and Strategies	• Start of new anti-cancer therapy PFS will be censored at the last evaluable post-baseline tumor assessment prior to start of new anti-cancer therapy (hypothetical strategy)
Key Secondary Estimand Description - PFS	
• HR of PFS between tarlatamab and SOC, for subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy, prior to start of new anti-cancer therapy (hypothetical strategy)	

Key Secondary - PRO	
• Compare the treatment effect of tarlatamab with SOC on Patient-reported disease-related symptoms, Physical Function, and Quality of Life	• Change from Baseline assessed 6-weekly over time to 18 weeks Chest Pain as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC-QLQ-LC13) Cough as measured by EORTC-QLQ-LC13 Dyspnea as measured by EORTC Cancer Quality of Life Questionnaire 30 (EORTC-QLQ-C30) and EORTC-QLQ-LC13 Physical Function as measured by EORTC-QLQ-C30 Global Health Status of life as measured by EORTC-QLQ-C30
Attributes	**Key Secondary Estimand: PRO**
• Target Population	• Subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy
• Key Secondary Endpoint	• Patient-reported outcome (PRO)
• Summary Measures	• Change from Baseline assessed 6-weekly over time to 18 weeks
• Intercurrent Events and Strategies	• Discontinuation of treatment • PRO measurements before or on discontinuation of treatment will be used to estimate treatment effect (hypothetical strategy)
Key Secondary Estimand Description – PRO	
• Change from Baseline assessed 6-weekly over time to 18 weeks in PRO endpoints between tarlatamab and SOC, for subjects with relapsed small cell lung cancer after platinum-based first-line chemotherapy. PRO measurements before or on discontinuation of treatment will be used to estimate treatment effect (hypothetical strategy)	
Secondary	
• Compare the efficacy of tarlatamab with SOC as assessed by PFS at 1 year from randomization, objective response (OR), disease control (DC), and duration of response (DOR) based on investigator assessment per RECIST 1.1, and OS at 1 year, 2 years, and 3 years from randomization	• OR, defined as best overall response (BOR) of complete response (CR) + partial response (PR) • DC, defined as CR + PR + stable disease (SD) • DOR, defined as the time from the first documentation of OR until the first documentation of disease progression or death due to any cause, whichever occurs first. Only subjects who have achieved OR will be evaluated for DOR • PFS rate at 1 year from randomization

	• OS rate at 1 year, 2 years, and 3 years from randomization
• Compare the safety and tolerability of tarlatamab with SOC	• Incidence of treatment-emergent adverse events including grade ≥ 3 treatment-emergent adverse events, serious treatment-emergent adverse events, treatment-emergent adverse events leading to treatment discontinuation, fatal treatment-emergent adverse events, and treatment-related adverse events
• Characterize the pharmacokinetics (PK) of tarlatamab	• Serum concentrations of tarlatamab
• Evaluate the immunogenicity of tarlatamab	• Incidence of anti-tarlatamab antibody formation
• Compare the treatment effect of tarlatamab with SOC on remaining PRO measures	• Time to deterioration (TTD) for symptom scales Chest Pain as measured by EORTC-QLQ-LC13 Cough as measured by EORTC-QLQ-LC13 Dyspnea as measured by EORTC-QLQ-C30 and EORTC-QLQ-LC13 • Change from Baseline assessed 6-weekly over time to 18 weeks Pain as measured by Brief Pain Inventory - Short Form (BPI-SF) Remaining domains for QLQ-C30 and QLQ-LC13 Patient Global Impression of Severity (PGIS) (overall and for each symptom included in key secondary) Patient Global Impression of Change (PGIC) (overall and for each symptom included in key secondary) • Summary scores at each assessment and change from baseline of visual analogue scale (VAS) score as measured by 5-level EuroQol-5 Dimension (EQ5D-5L)
• Evaluate the severity and impact of symptomatic toxicity of tarlatamab and SOC	• Comparison of responses to selected questions from the PRO-CTCAE item bank • A single question from FACT-G on symptom bother

4. Study Design

4.1 Overall Design

This is an open-label, randomized, multi-center, phase 3 study that will evaluate efficacy and safety of tarlatamab (AMG 757) compared with SOC therapy for the treatment of subjects with SCLC who have progressed after 1 prior line of platinum-containing therapy.

The study consists of a 21-day screening period, a treatment period, an SFU visit, and an LTFU period.

Subjects will be randomized with a 1:1 allocation ratio to receive tarlatamab or SOC therapy (lurbinectedin or topotecan in US, Canada, Australia, Singapore, Korea; amrubicin in Japan; topotecan in all countries except Japan).

Randomization will be stratified by:

- Prior anti-PD-1 or prior anti-PD-(L)1 exposure (yes vs no)
- Chemotherapy-free interval (≥ 180 days; < 180 to ≥ 90 days; < 90 days)
- Presence (previous or current) of brain metastases (yes or no)
- Standard of care (topotecan/amrubicin vs lurbinectedin)

Chemotherapy-free interval is defined as the number of days elapsed between the last dose of prior chemotherapy and the date of first suspicion of disease relapse or progression (clinical or radiological). For example, if a patient experiences seizure and a brain metastasis progression is detected 48-hours after the seizure occurred, the date of progression is the date of this first seizure episode. Additionally, global enrollment will be monitored in order to ensure the majority of subjects have prior anti-PD-(L)1 exposure. **For patients with no exposure to prior anti-PD-(L)1, the reason for nonuse will be collected.**

Study treatment will be administered as follows:

- Tarlatamab will be administered as a 60-minute intravenous (IV) infusion with a step dose (1 mg tarlatamab) on cycle 1 day 1 (C1D1) followed by 10 mg target dose on C1D8 and C1D15, and Q2W thereafter (ie, C2+ D1/D15 dosing) in a 28-day cycle.
    - Monitoring - cycle 1: Monitoring required for 6 to 8 hours post-infusion at C1D1 and C1D8.
        - Cohabitant (caregiver) support for 24 hours post-infusion and the ability to stay within 1 hour of a hospital for 24 hours is required.
        - Counseling the subject and caregiver on signs and symptoms of CRS and ICANS by a health care provider is required prior to discharge.

- Subjects return to site on cycle 1 day 2 and cycle 1 day 9 for vital signs and physical examination.
- At subsequent visits, additional monitoring may be required post-infusion. Refer to Section 6.1.1 (Table 6-1).

- Pre- and post-infusion medication requirements:
  - Dexamethasone: 8 mg IV (or equivalent) will be administered within 1 hour prior to tarlatamab infusion on C1D1 and C1D8
  - IV hydration: 1 L normal saline over 2 to 4 hours following tarlatamab doses on C1D1 and C1D8

- Standard of care (21-day cycle): Standard of care will be administered as follows in a 21-day cycle:
  - Lurbinectedin (US, Canada, Australia, Singapore, and Korea) will be administered as 3.2 mg/m^2 IV on day 1 every 3 weeks
  - Topotecan (all countries, except Japan and China) will be administered as IV at 1.5 mg/m^2 or oral at 2.3 mg/m^2/day on days 1, 2, 3, 4, and 5 every 3 weeks
  - Topotecan (China mainland [China mainland in this clinical study shall be referred to as "China"]) will be administered as IV at 1.2 mg/m^2 or other locally approved dose or oral at 2.3 mg/m^2/day on days 1, 2, 3, 4, and 5 every 3 weeks
  - Amrubicin (Japan) will be administered as 40 mg/m^2 IV on days 1 to 3 every 3 weeks

Subjects will receive study treatment until investigator-determined radiographic disease progression per RECIST 1.1, unacceptable toxicity, withdrawal of consent, death, or end of study as determined by the sponsor (whichever occurs first). Following documented radiographic progression, the subject may remain on study treatment provided criteria are met. Refer to Section 6.1.7 for more details.

Upon permanent discontinuation from study treatment for any reason, an SFU visit will be performed approximately **60** (+5) days after last dose of study treatment, even if subsequent anti-cancer therapy has been initiated within that period.

After the SFU visit, subjects will be followed in LTFU for survival every 12 weeks (± 14 days) from the SFU visit (or last imaging visit, whichever is later) for up to 3 years after the last subject is enrolled, or 1 year from the subject's last dose of study treatment, whichever is later. **Ad hoc vital status (survival status) collection may be required to support key study analysis.**

Approximately [redacted] subjects will be enrolled at approximately 240 sites globally. The median time of subject's participation in the study treatment period will be approximately 4 to 6 months with median study duration to be approximately 9 to 12 months. The total study duration is expected to be approximately 4 years from the first subject enrolled to

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

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

4.2 Patient Input into the Study Design

Web-enabled ethnographic immersion interviews were conducted as part of Study 20200491 with patients with diverse SCLC and caregivers located in the US. Their feedback has been incorporated into Table 6-1 (Monitoring Guidance).

4.3 Justification for Dose

4.3.1 Justification for Investigational Product Dose

The study will evaluate a tarlatamab target dose level of 10 mg IV administered as a Q2W regimen. To mitigate the risk of CRS, tarlatamab treatment will be initiated at a lower step dose of 1 mg on cycle 1 day 1, followed by the target dose (10 mg IV) on cycle 1 day 8, cycle 1 day 15, and Q2W thereafter. Both the step dose and target dose are administered as a 60-minute infusion. This regimen was selected based on the totality of available safety, tolerability, pharmacokinetics (PK), and preliminary efficacy data from the dose exploration and expansion phase of the FIH Study 20160323 in subjects with SCLC that evaluated a target dose range of 0.003 mg to 100 mg administered as a Q2W regimen. In addition, this regimen is also informed by the safety and efficacy data from an ongoing phase 2 study in subjects with SCLC that evaluated 2 active dose levels of 10 mg and 100 mg administered Q2W using a step dose of 1 mg. Based on a pre-specified IA in part 1 of the phase 2 Study 20200491 the regimen using 10 mg target dose with a 1 mg step dose was selected as the monotherapy recommended phase 2 dose (RP2D) regimen to balance the efficacy/safety of tarlatamab and to be further evaluated in part 2 and part 3 of the phase 2 Study 20200491, and any subsequent studies for tarlatamab. The primary analysis for the phase 2 Study 20200491 reinforced the selection of 10 mg target dose for tarlatamab studies.

4.3.1.1 Selection of Cycle 1 Day 1 step dose of 1 mg

Tarlatamab will be infused over 60 minutes at the selected step dose of 1 mg. Cytokine release syndrome is an identified risk of tarlatamab caused by T cell-mediated cytokine release. Based on 1 grade 2 CRS event observed in the 1 mg target dose cohort, in the FIH Study 20160323, a mitigation measure was implemented to improve the CRS profile to include a one-step dosing in cycle 1 (lower step dose prior to reaching the target

dose). A dose of 1 mg was selected as the initial step dose on cycle 1 day 1 to aid in escalation to higher target doses starting on cycle 1 day 8 in order to mitigate the risk of CRS.

Available safety and tolerability data from the dose exploration and expansion phase of Study 20160323, which evaluated the target dose range of 10 to 100 mg administered over 60-minute infusion, supports the use of lower step dose of 1 mg on cycle 1 day 1.

Tarlatamab has demonstrated durable antitumor activity in subjects with ES-SCLC in a phase 2 (Study 20200491) and phase 1 study (Study 20160323) with a favorable benefit/risk profile. Please refer to the Investigator's Brochure for the most current efficacy and safety data across the tarlatamab program.

4.3.1.2 Selection of the target dose of 10 mg starting Cycle 1 Day 8, Day 15 and Q2W thereafter

The selection of the planned 10 mg target dose level to be evaluated in this study is informed by the totality of the available safety, tolerability, and preliminary anti-tumor activity and efficacy data from the FIH Study 20160323 and Part 1 of the ongoing phase 2 Study 20200491.

In the FIH Study 20160323, acceptable safety profile has been demonstrated for tarlatamab across a dose range of 0.003 to 100 mg. As of 19 July 2022, 10 subjects enrolled to the 10 mg target dose level have received at least 1 dose of tarlatamab. Two (20%) subjects experienced grade 2 CRS (no grade 3 or above CRS was observed), 2 (20%) subjects had grade 3 or higher treatment-related adverse events, and 1 (10%) subject had treatment-related serious adverse events reported. Of the 23 subjects enrolled to the 100 mg target dose level (cohorts 10 and 11) with the 1 mg step dose on C1D1, 3 (13%) subjects experienced grade 2 CRS (no grade 3 or above CRS was observed), 10 (43%) subjects had grade 3 or higher treatment-related adverse events, and 8 (35%) subjects had treatment-related serious adverse events reported (Paz-Ares et al, 2023).

Data from the dose exploration and expansion phase of the FIH Study 20160323 supported evaluation of 2 active target dose levels of 10 mg and 100 mg Q2W to be further characterized in the phase 2 Study 20200491. This phase 2 Study 20200491 incorporated a randomized dose part (Part 1) and a dose expansion part of the dose selected in Part 1 (Part 2). An interim analysis was planned to review efficacy data so as to inform the dose selection for the expansion part (Part 2) of the phase 2 trial and the phase 3 trial Study 20210004.

Safety, efficacy, dose-response, and exposure-response analysis were performed for key safety and efficacy variables using data from Part 1 of the phase 2 study at a pre-specified interim analysis evaluated by a specifically designated team of independent scientists who were unblinded to the data. Based on these analyses, the 10 mg regimen using a step-dose of 1 mg was selected as the target dose to be further evaluated in Part 2 of the phase 2 study as well as in this phase 3 Study 20210004 protocol.

4.3.2 Justification for Non-investigational Product/Auxiliary Medicinal Product Dose

SOC chemotherapy (lurbinectedin or topotecan [US, Canada, Australia, Singapore, and Korea], and topotecan [all countries, except Japan] will be administered per the regional prescribing information. Amrubicin [Japan] will be administered per the regional prescribing information and local guidelines). Refer to Section 6.1.1.1 for additional information.

4.4 Justification for Monitoring

Safety data from clinical Study 20200491 has confirmed that the most common adverse event with tarlatamab is CRS (Ahn et al, 2023). Cytokine release syndrome most frequently occurs after the first two infusions of tarlatamab (cycle 1 day 1 and cycle 1 day 8), is mostly grade 1 to 2 in nature and rarely develops rapidly. The subject incidence of CRS at the 10 mg dose in Study 20200491 was 30.1% (40/133) grade 1, 20.3% (27/133) grade 2 and 0.8% (1/133) grade 3. There were no grade 4 or 5 CRS events in this study. This profile enables reduction of mandatory hospital monitoring [redacted] Importantly, patients will return to study sites on the day following these infusions for clinical evaluation [redacted] Additional detailed guidance for CRS monitoring and mitigation during and following these treatment visits is outlined in protocol Schedule of Activities (Section 1.3) and Section 6.1.

4.5 End of Study

An individual subject is considered to have completed the study if they have completed the last visit shown in the Schedule of Activities (Section 1.3).

The median study duration for individual subjects is to be approximately 9 to 12 months, including the LTFU. Safety follow-up visit should occur at approximately **60** (+ 5) days, even if subsequent anti-cancer therapy has been initiated within that period. Long-term follow up assessments will also be conducted by clinic visit, telephone, or chart review to assess for survival and/or the commencement of subsequent cancer therapy every 12 weeks (± 14 days) from the SFU visit (or last imaging visit, whichever is later) for up to 3 years after the last subject is enrolled, or 1 year from the subject's last dose of study treatment, whichever is later. **Ad hoc vital status (survival status) collection may be required to support key study analysis.**

The actual duration for individual subjects will vary depending upon tolerability of tarlatamab or SOC chemotherapy, evidence of clinical and/or radiological disease progression, and willingness to participate in the study. Please see Section 7.1 for reasons for removal from treatment and Section 7.2.1 for reasons for removal from study.

The end of study date for the entire study 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, LTFU, antibody testing), as applicable.

5. Study Population

Approximately [redacted] subjects will be enrolled in the study across approximately 240 sites globally with 1:1 randomization to receive either tarlatamab or SOC chemotherapy.

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

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). This log may be completed and updated via Interactive Response Technology (IRT).

Eligibility criteria will be evaluated during screening **and prior to randomization**.

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

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

5.1 Inclusion Criteria

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

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

102 Age ≥ 18 years (or legal adult age within country, whichever is older) at the time of signing the informed consent.

110 Histologically or cytologically confirmed SCLC with demonstrated progression or relapse.

104 Subject has progressed or recurred following 1 platinum-based regimen:

- documented first disease progression must be during or following first-line platinum-based systemic chemotherapy for extensive stage (ES) or limited stage (LS) disease
- patients who received treatment for LS disease who recur are eligible
- patients who received adjuvant Platinum-Etoposide (EP) after resection of their SCLC who recur are eligible
- in countries where SOC first-line systemic treatment for ES disease includes platinum containing chemotherapy in combination with PD-(L)1 inhibitor, it is required that patients have failed PD-(L)1 inhibitor as part of their first-line systemic treatment or are ineligible to receive PD-(L)1 inhibitor therapy
- is a candidate for any of the 3 SOC therapies to be evaluated in this study as per investigator discretion

106 Measurable disease as defined per RECIST 1.1 within the 21-day screening period.

- Screening scans performed as SOC and prior to informed consent, may be used to confirm subject eligibility if completed within the 21-day screening period, provided that informed consent for the use of these scans is obtained prior to any transfer of data.

107 Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1.

108 Minimum life expectancy of 12 weeks.

112 Adequate organ function, defined as follows:

- Hematological function:
  - absolute neutrophil count ≥ 1.5 x 10^9/L
  - platelet count ≥ 100 x 10^9/L
  - hemoglobin > 9 g/dL (90 g/L)
- Coagulation function:
  - prothrombin time (PT)/international normalized ratio (INR) and partial thromboplastin time (PTT) or activated partial thromboplastin time (APTT) ≤ 1.5 x institutional upper limit of normal (ULN) except for subjects

undergoing new class anticoagulant therapy (eg, Edoxaban), stable dose for 2 weeks required prior to enrollment.

- Renal function:
  - estimated glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) calculation $>$ 30 mL/min/1.73 m^2
- Hepatic function:
  - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $<$ 3 x ULN (or $<$ 5 x ULN for subjects with liver involvement)

    total bilirubin (TBL) $<$ 1.5 x ULN (or $<$ 2 x ULN for subjects with liver involvement)
- Pulmonary function:
  - no clinically significant pleural effusion. Pleural effusion managed with indwelling pleural catheter (eg, PleurX) are allowed

    baseline oxygen saturation $>$ 90% on room air
- Cardiac function:
  - cardiac ejection fraction $\geq$ 50%, no clinically significant pericardial effusion as determined by an echocardiogram (ECHO) or multigated acquisition (MUGA) scan, and no clinically significant electrocardiogram (ECG) findings

5.2 Exclusion Criteria

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

Disease Related

238 Symptomatic central nervous system (CNS) metastases:

- Subjects with treated brain metastases are eligible provided the following criteria are met:

- Subjects with untreated brain metastases that are asymptomatic and do not require corticosteroids, nor local therapy per investigators standard of practice are allowed

202 Diagnosis or evidence of leptomeningeal disease.

203 Prior history of immune checkpoint inhibitors resulting in:

- Any severe or life-threatening immune-mediated adverse event

- History of immune-mediated encephalitis or other immune-mediated CNS event (any grade)
- Grade ≥ 2 immune-mediated recurrent pneumonitis
- Infusion-related reactions leading to permanent discontinuation of immunotherapy agent

Exception: Subjects with a history of immune checkpoint inhibitor-induced endocrinopathy which is clinically stable on replacement therapy.

Other Medical Conditions

204 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.

205 History of solid organ transplantation.

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

- low-risk malignancy treated with curative intent and with no known active disease present for ≥ 1 year before enrollment and believed to be at low risk for recurrence per investigator discretion.
- 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.

207 Myocardial infarction and/or symptomatic congestive heart failure (New York Heart Association > class II) within 12 months prior to first dose of study treatment (Section 11.9).

208 History of arterial thrombosis (eg, stroke or transient ischemic attack) within 12 months prior to first dose of study treatment.

239 Presence/history of viral infection:

Human immunodeficiency virus (HIV) infection

- Subjects with HIV infection on antiviral therapy and undetectable viral load are permitted with a requirement for regular monitoring for reactivation for the duration of treatment on study per local or institutional guidelines,

Active hepatitis C infection (subjects with detectable hepatitis C antibody [HCV Ab] and HCV RNA viral load above the limit of quantification),

- Subjects with presence of HCV Ab and HCV RNA viral load below the limit of quantification (HCV RNA negative) with or without prior treatment are allowed

Active hepatitis B infection (presence of hepatitis B surface antigen [HBsAg] and hepatitis B virus [HBV] DNA viral load above the limit of quantification [HBV DNA positive])

- Subjects with resolved HBV infection defined as absence of HBsAg and presence of HBV core antibody (anti-HBc) followed by an HBV DNA viral load below the limit of quantification (HBV DNA negative) are allowed, with a requirement for regular monitoring for reactivation for the duration of treatment on the study and assessing the need for HBV prophylaxis therapy per local or institutional guidelines.
- Subjects with chronic HBV infection inactive carrier state defined as presence of HBsAg and HBV DNA viral load below the limit of quantification [HBV DNA negative] are allowed, with a requirement for regular monitoring for reactivation for the duration of treatment on the study and assessing the need for HBV prophylaxis therapy per local or institutional guidelines.

210 Receiving systemic corticosteroid therapy or any other form of immunosuppressive therapy within 7 days prior to first dose of study treatment:

- Prophylactic dexamethasone required by the protocol and any anti-emetic therapies are allowed
- Low-dose corticosteroids (prednisone ≤ 10 mg per day or equivalent is permitted during the trial)

211 Subject with symptoms and/or clinical signs and/or radiographic signs that indicate an acute and/or uncontrolled active systemic infection within 7 days prior to the first dose of study treatment.

- Subject has known active infection requiring parenteral antibiotic treatment. Upon completion of parenteral antibiotics and resolution of symptoms, the subject may be considered eligible for the study from an infection standpoint.
- Note: Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment. Subjects requiring oral antibiotics who have been afebrile for > 24 hours, have no leukocytosis, nor clinical signs of infection are eligible. Screening for chronic infectious conditions is not required unless otherwise noted as exclusion criteria.

212 Evidence of interstitial lung disease or active, non-infectious pneumonitis.

Prior/Concomitant Therapy

237 Prior therapy with tarlatamab or any of the SOC chemotherapy included as part of this trial, or participation in any tarlatamab clinical trial.

214 Prior therapy with any selective inhibitor of the DLL3 pathway.

215 Subject received more than 1 prior systemic therapy regimen for SCLC (EP/anti-PD-[L]1 therapy followed by anti-PD-[L]1 maintenance therapy is considered 1 regimen).

216 Prior anti-cancer therapy within 21 days prior to first dose of study treatment.

Exceptions:

- Subjects who received conventional chemotherapy are eligible if at least 14 days have elapsed and if all treatment-related toxicity has been resolved to grade ≤ 1, or to levels dictated in the eligibility criteria, before first dose of study treatment, with the exception of alopecia or toxicities considered

irreversible (defined as having been present and stable for > 30 days) which are not otherwise described in the exclusion criteria.

- Prior palliative radiotherapy must have been completed at least 7 days before the first dose of study treatment.

217 Receiving anti-cancer therapy such as chemotherapy, immunotherapy, or targeted therapy. Patients who are receiving adjuvant hormonal therapy for resected breast cancer may be eligible (refer also to exclusion related to history of other malignancies).

218 Any herbal or prescription/non-prescription medications known to inhibit membrane transporters P-glycoprotein (P-gp) and/or breast cancer resistance protein (BCRP) (including but not limited to cyclosporine, clarithromycin, itraconazole, or ketoconazole) within 7 days prior to the first dose of study treatment.

219 Any herbal or prescription/non-prescription medications known to be moderate or strong inhibitors of cytochrome P450 3A (CYP3A) enzymes (including but not limited to clarithromycin, itraconazole, ketoconazole) within 7 days prior to the first dose of study treatment.

220 Any herbal or prescription/non-prescription medications known to be moderate or strong inducers of CYP3A enzymes (including but not limited to efavirenz, phenobarbital, phenytoin, rifampin, St John's Wort) within 28 days prior to first dose of study treatment.

221 Subjects who have reached the limit dose of prior treatment with cardiotoxic drugs such as other anthracyclines (the total dose of daunorubicin hydrochloride is 25 mg/kg body weight, the total dose of doxorubicin hydrochloride is 500 mg/m^2 body surface area [BSA], the total dose of epirubicin hydrochloride is 900 mg/m^2 BSA, the total dose of pirarubicin hydrochloride is 950 mg/m^2 BSA, etc,).

222 Major surgical procedures within 28 days prior to first dose of study treatment.

223 Treatment with live virus, including live-attenuated vaccination, within 14 days prior to the first dose of study treatment. Inactive vaccines (eg, non-live or non-replicating agent) and live viral non-replicating vaccines (eg, Jynneos for Monkeypox infection) within 3 days prior to first dose of study treatment.

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

240 Any previous diagnosis of transformed non-small cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR) activating mutation positive NSCLC that has transformed to SCLC.

- Subjects with mixed histology tumors with predominant SCLC histology are allowed.

Other Exclusions

226 Female subjects of childbearing potential unwilling to use protocol specified method of contraception see Appendix 5 (Section 11.5) during treatment and for an additional **60** days after the last dose of tarlatamab (Note: contraception requirements for SOC therapies are based on regional prescribing information).

227 Female subjects who are breastfeeding or who plan to breastfeed while on study through **60** days after the last dose of tarlatamab (Note: breastfeeding restrictions for SOC therapies are based on regional prescribing information).

228 Female subjects planning to become pregnant or donate eggs while on study through **60** days after the last dose of tarlatamab (Note: contraception requirements for SOC therapies are based on regional prescribing information).

229 Female subjects of childbearing potential with a positive pregnancy test assessed at screening by a serum pregnancy test.

230 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 **60** days after the last dose of tarlatamab. Refer to Appendix 5 (Section 11.5) for additional contraceptive information (Note: contraception requirements for SOC therapies are based on regional prescribing information).

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

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

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

234 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.

235 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 Medical Monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Meals and dietary restrictions are not applicable for tarlatamab. For SOC chemotherapy, refer to regional prescribing information and/or relevant local guidelines.

5.3.2 Caffeine, Alcohol, and Tobacco

Caffeine, alcohol, and tobacco limitations are not applicable for tarlatamab. For SOC chemotherapy, refer to regional prescribing information and/or relevant local guidelines.

5.3.3 Activity

Not applicable.

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

Each subject who consents to the study receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by IRT. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The 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. This number will not necessarily be the same as the randomization number assigned for the study.

Subjects are eligible to be enrolled in the study when the investigator confirms that the subject has met all eligibility criteria. Subjects are considered enrolled at the time of randomization, defined as successful randomization transaction via IRT. The investigator is to document enrollment decision and date, in the subject's medical record and in/on the Subject Enrollment case report form (CRF) via IRT.

Enrollment into the SOC arm will be monitored in order to ensure an appropriate distribution of subjects into each of the SOC treatments and an appropriate proportion of anti-PD-(L)1 exposed subjects.

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

5.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the main clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times. Refer to Section 8.1.1.

6. Study Intervention

Study intervention is defined as any investigational product(s), noninvestigational product(s)/auxiliary medicinal 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 according to local regulations in several countries, investigational product(s) described in Section 6.1.1 are referred to as investigational medicinal product(s) and noninvestigational product(s) described in Section 6.1.2 are referred to as non-investigational medicinal product(s).

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

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 6-1. Investigational Products

Study Treatment Name	Amgen Investigational Product:[a] Tarlatamab
Dosage Formulation	Tarlatamab is supplied as a sterile, single-use, preservative free lyophilized drug product containing 1 or 10 mg of tarlatamab per vial. Tarlatamab is intended for reconstitution with sterile water for injection and dilution in an IV bag with normal saline (0.9% sodium chloride) and an IV solution stabilizer. The drug product is formulated with L glutamic acid, sucrose, polysorbate 80, pH 4.2.
Unit Dose Strength(s) **Dosage Levels and Dosage Frequency**	1 mg step dose on cycle 1 day 1 10 mg target dose starting cycle 1 day 8, cycle 1 day 15, and Q2W thereafter
Route of Administration	IV infusion
Accountability	The dose, start date/time, stop date/time, and lot number of tarlatamab, are to be recorded on each subject's eCRF(s).
Dosing Instructions	Tarlatamab will be administered as an IV infusion for 60 minutes (± 10 minutes) followed by a slow bolus flush. Investigational products will be administered at the study center by a qualified staff member. A physician must be available at the time of administration of investigational products.

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Footnotes defined on last page of this table.

Study Treatment Name	Amgen Investigational Product:[a] Tarlatamab
Monitoring Guidance	– Cycle 1 Day 1 and Cycle 1 Day 8: ○ Subject will remain at study site for 6 to 8 hours post-infusion at C1D1 and C1D8. Cohabitant (caregiver) support for 24 hours post-infusion and the ability to stay within 1 hour of a hospital for 24 hours is required. ○ Subjects may be discharged after the required monitoring period if there are no signs and symptoms of CRS, ICANS, or other acute toxicities according to the discretion of the treating physician. Counseling the subject and caregiver on signs and symptoms of CRS and ICANS by a health care provider is required prior to discharge. – Subjects return to site on cycle 1 day 2 and cycle 1 day 9 for vital signs and physical examination. – Monitoring for subsequent treatment visits is at the discretion of the investigator if asymptomatic and clinically stable. Consider monitoring if the subject experiences a grade ≥ 2 CRS, any grade ICANS, or any grade ICANS-related neurologic[b] adverse events at the immediate prior treatment (ie, following the dose given at the prior visit). – **Cycle 2+** ○ **Additional monitoring may be recommended post-infusion based on occurrence of CRS, ICANS, or ICANS-related neurological events.** In the event of an extended study treatment interruption (see Table 6-3), subjects are required to be monitored according to cycle 1 monitoring guidance.

C1D1 = cycle 1 day 1; C1D8 = cycle 1 day 8; CRS = cytokine release syndrome; eCRF = electronic case report form; IV = intravenous; ICANS = immune effector cell-associated neurologic syndrome; Q2W = every 2 weeks.

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

[b] ICANS-related neurologic adverse events per discretion of investigator, which may include, but are not limited to: confusion, delirium, encephalopathy, apraxia, ataxia, neurotoxicity, seizure, tremor, dysgraphia, expressive aphasia, depressed level of consciousness, or impaired attention.

6.1.1.1 Standard of Care Treatment Options

In some regions, SOC chemotherapy administered for preventative, diagnostic, or therapeutic reasons, may be considered noninvestigational medicinal products.

6.1.1.1.1 Lurbinectedin

Lurbinectedin will be dosed at the approved regimen of 3.2 mg/m^2 on day 1 of each 21-day cycle. Lurbinectedin will be administered as an IV infusion for 60 minutes (± 10 minutes).

Where supplied by Amgen, **information regarding** lurbinectedin formulation and dose **preparation will be provided to the site**. Where supplied locally, refer to the regional prescribing information.

The dose, start date/time, and stop date/time are to be recorded on each subject's electronic case report forms (eCRFs). Product lot number will be retained as part of the site level records.

Refer to the regional manufacturer prescribing information for lurbinectedin dosing, dose adjustments, administration and for additional information.

6.1.1.1.2 Topotecan

Topotecan will be dosed at 1.5 mg/m^2 IV, with the exception of China, which will dose at 1.2 mg/m^2 IV or other locally approved dose or 2.3 mg/m^2/day oral on days 1, 2, 3, 4, and 5 of each 21-day cycle. Topotecan Injection will be administered as an IV infusion over 30 minutes (± 5 minutes). Topotecan capsules should be swallowed whole. Do not chew, crush, or divide capsules. If the dose is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose at the scheduled time.

Topotecan **may be** supplied by Amgen **or locally supplied by sites**. Where supplied by Amgen, **information regarding topotecan formulation and dose preparation will be provided to the site.** Topotecan capsules are expected to be locally sourced per local practice and regulation. Refer to the regional prescribing information for product details. Subjects will be instructed to take their oral topotecan dose in the clinic after all pre-dose assessments have been performed during day 1 of each cycle. For days 2, 3, 4, and 5 of the cycle, subjects can take their oral topotecan dose at home, if deemed appropriate by the investigator.

The dose, start date/time, and stop date/time are to be recorded on each subject's eCRF(s). Additional dosing information **should** be collected through a web-based diary when subjects self-administer oral topotecan at home. Product lot number will be retained as part of the site level records.

Refer to the regional manufacturer prescribing information for topotecan dosing, dose adjustments, administration and for additional information.

6.1.1.1.3 Amrubicin

Amrubicin will be dosed at the guideline recommended regimen of 40 mg/m^2 (Guidelines for Diagnosis and Treatment of Lung Cancer in Japan, 2023) and will be administered as an IV infusion over 5 to 15 minutes on days 1 to 3 of each 21-day cycle. Prophylactic use of granulocyte colony-stimulating factor (G-CSF) is allowed, with investigator's discretion.

Where supplied by Amgen, **information regarding** amrubicin **formulation and dose preparation will be provided to the site**.

The dose, start date/time, and stop date/time are to be recorded on each subject's eCRF(s). Product lot number will be retained as part of the site level records.

Refer to the regional prescribing information for amrubicin dosing, dose adjustments, administration and for additional information.

6.1.2 Noninvestigational/Auxiliary Medicinal Products

In some regions, the investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) described in Section 6.1.1.1 and administered for preventative, diagnostic, or therapeutic reasons, may be considered noninvestigational medicinal products.

All other noninvestigational product(s)/auxiliary medicinal product(s) including, tarlatamab pre- and post-infusion medication (dexamethasone and IV hydration) and standard of care (SOC) chemotherapy co-medications, that are commercially available are not provided by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these noninvestigational product(s)/auxiliary medicinal product(s).

6.1.3 Medical Devices

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

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

6.1.3.1 Tarlatamab Pre- and Post-infusion Medications

Dexamethasone

Dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) will be administered within 1 hour prior to tarlatamab infusion on days 1 and 8 of cycle 1.

IV Hydration

Prophylaxis with IV hydration (1 L normal saline over 2 to 4 hours) will be administered immediately following tarlatamab doses on cycle 1 day 1 and day 8.

6.1.3.2 Standard of Care Co-medications

Refer to the regional prescribing information or institutional guidelines (if not addressed in prescribing information) for additional information regarding SOC co-medications.

6.1.3.3 Cytokine Release Syndrome Rescue Medication

All sites will ensure that CRS rescue medications are available on-site, including corticosteroids and (for sites in regions where tocilizumab is approved and available) sites are required to have tocilizumab or siltuximab (if tocilizumab is not available) on site for potential treatment of CRS **prior to dosing subjects in the Tarlatamab arm**.

Refer to the regional prescribing information or institutional guidelines (if not addressed in prescribing information) for additional information regarding rescue medication.

6.1.4 Other Intervention Procedures

There are no other intervention procedures in this study.

6.1.5 Product Complaints

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

This includes any investigational/noninvestigational product(s)/auxiliary medicinal product(s), provisioned and/or repackaged/modified by Amgen (ie, tarlatamab, lurbinectedin, topotecan, amrubicin, tocilizumab, or siltuximab).

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

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

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

- Other investigational agents, devices (other than those specified in the protocol) and procedures are prohibited while on study treatment.
- Anticancer therapies other than those specified in the protocol are prohibited while on study treatment.
- Radiation therapy
  - Exception: Radiation therapy for symptom control (eg, bone metastasis) or brain metastasis treatment may be allowed after discussion with the medical monitor. The radiation therapy should not include the thoracic field and must have been completed at least 7 days before the subsequent dose of tarlatamab.
- 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 investigator and medical monitor.
- During tarlatamab treatment: Live and live-attenuated vaccines are prohibited for the duration of tarlatamab treatment.
  - Live viral non-replicating vaccine (eg, Jynneos for Monkeypox infection) is allowed when administered > 3 days before or > 3 days after a tarlatamab infusion.
  - Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed when administered > 3 days before or > 3 days after a tarlatamab infusion. However, intranasal influenza vaccines (eg, Flu - Mist®) are live attenuated vaccines, and are not allowed at any time during tarlatamab treatment.
  - Vaccinations for COVID-19 (SARS-CoV-2 vaccination) are generally not live or live-attenuated and are allowed when administered > 3 days before or > 3 days after a tarlatamab infusion.
- After completion of tarlatamab treatment: Live and live-attenuated vaccines are prohibited for a further **60** days after last dose.
- Vaccination exclusions, restrictions, and precautions for SOC therapies are based on regional prescribing information or institutional guidelines (if not addressed in prescribing information).

- Subjects must not schedule any major elective surgery during the treatment period and for at least 30 days after the last administration of study drugs. If a subject undergoes any unexpected surgery during the course of the study, all study treatments must be withheld, and the investigator or designee should notify the sponsor's medical monitor as soon as possible. A subject may be allowed to resume study drugs if both the investigator and sponsor's medical monitor agree to restart study therapy.
- Subjects randomized to SOC, who are allocated to receive oral or IV topotecan, are not allowed to use any of the following for the duration of the study treatment:
  - Any herbal or prescription/non-prescription medications known to be inhibitors of membrane transporters P-gp and BCRP (including but not limited to cyclosporine, clarithromycin, itraconazole, ketoconazole or grapefruit juice or grapefruit-containing products).
- Subjects randomized to SOC, who are allocated to receive lurbinectedin, are not allowed to use any of the following for the duration of the study treatment:
  - Any herbal or prescription/non-prescription medications known to be moderate or strong inhibitors of CYP3A enzymes (including but not limited to clarithromycin, itraconazole, ketoconazole).
  - Any herbal or prescription/non-prescription medications known to be moderate or strong inducers of CYP3A enzymes (including but not limited to efavirenz, phenobarbital, phenytoin, rifampin, St John's Wort).
- Subjects randomized to SOC, who are allocated to receive amrubicin, are not allowed to use any cardiotoxic drugs such as other anthracyclines if they have reached the dose limit of prior treatment with these drugs.

6.1.7 Continuation on Investigational Product Treatment After First Radiologic Disease Progression

This section details the conditions necessary to allow continued study treatment **(Tarlatamab or SOC)** after first disease progression in subjects that, in the investigator's judgment, continue to have clinical benefit. All of the following criteria must be met:

- Subject continues to have clinical benefit per the investigator's judgment.
- Subject has stable ECOG PS.
- 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 (previous or current) of brain metastases (yes or no) is allowed provided the lesions are amenable to radiation therapy or dexamethasone (or corticosteroid equivalent), and the subject is clinically stable in the investigator's judgment.
- Subject continues to tolerate study drug.
- No other treatment discontinuation criteria are met (Table 6-2 and Section 11.7).
- No significant, unacceptable, or irreversible toxicities related to any dose of the study treatment or treatment related adverse events of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 at the current dose at the time of progression.

- **If r**adiation therapy is required**, it** must not include the thoracic field. Palliative radiation and/or surgery for new, progressive, or symptomatic lesions is permitted. Study treatment must be held during either treatment (radiation and/or surgery) and the treatment must be completed at least 7 days before the subsequent dose of study treatment.

Subjects **who are eligible to remain on study treatment after first progression** should perform all protocol-required procedures as noted in the Schedule of Activities (Section 1.3; imaging, labs, and clinic visits) per clinical judgment and if clinically indicated.

For subjects who continue treatment beyond radiologic progression, the first date of progression will be used for OR/ORR/DOR and progression-free survival analysis, and the subject's response post-first progression will not be used to evaluate objective response endpoints.

6.2 Dose Modification

6.2.1 Dose-Group/Cohort Study Escalation/De-escalation and Stopping Rules

Not applicable.

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

6.2.2.1 Amgen Investigational Product: Tarlatamab

The reason for tarlatamab delay or discontinuation is to be recorded on each subject's CRF. Tarlatamab will be discontinued or temporarily delayed in the event of a toxicity that, in the opinion of the investigator, warrants the discontinuation or dose reduction. For treatment interruptions, delays, and discontinuations, refer to tarlatamab guidance in Table 6-2.

Table 6-2. Tarlatamab Dose Modification Guidelines for Adverse Events

Grade	Description of Severity	Interruption/Delay	Specific Management	Restart guidance	Permanent Discontinuation
Neurologic Events					
1	Reference Section 11.11.2 for grading and management guidelines	No additional guidance	Follow institutional guidelines for management and per local practice: Consider diagnostic workup for alternate diagnosis [f] Supportive Care	No additional guidance	No additional guidance
2		No additional guidance	Follow institutional guidelines for management and administer corticosteroids per local practice: Consider diagnostic workup for alternate diagnosis [f] Reference dose of corticosteroids for grade 2 ICANS[f]: Dexamethasone 8 mg to 10 mg IV every 12 hours or methylprednisolone equivalent. Once ICANS improves to grade 1 or less, taper and or stop corticosteroids depending on clinical situation	No additional guidance	No additional guidance
3		Delay tarlatamab until the event improves to grade ≤ 1	Follow institutional guidelines for management and administer corticosteroids per local practice: Consider diagnostic workup for alternate diagnosis [f] Consider ICU transfer Reference dose of corticosteroids for grade 3 ICANS [f]: Dexamethasone 10 mg IV every 6 hours or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Once ICANS improves to grade 1 or less, taper and or stop corticosteroids depending on clinical situation	Resume tarlatamab no less than 72 hours after the initial observation of the grade 3 adverse event	• Initial grade 3 neurologic event does not improve to grade ≤ 1 within 7 days, OR • Grade 3 neurologic event reoccurs within 7 days of resuming tarlatamab

Abbreviations and footnotes defined on last page of table

Table 6-2. Tarlatamab Dose Modification Guidelines for Adverse Events

Grade	Description of Severity	Interruption/Delay	Specific Management	Restart guidance	Permanent Discontinuation
Neurologic Events					
4		Immediately stop any ongoing infusion	Follow institutional guidelines for management and administer corticosteroids per local practice: Consider diagnostic workup for alternate diagnosis[f] Transfer to ICU Reference dose of corticosteroids for grade 4 ICANS [f]: Methylprednisolone 1000 mg/day in divided doses IV for 3 days followed by taper as clinically indicated. Consider additional therapies per guidelines.	Permanently discontinue	Permanently discontinue
Seizure	Reference Section 11.11.2 for grading and management guidelines	Delay tarlatamab until the event improves to grade $\leq$ 1[g]	Administration of corticosteroids and anti-seizure medication is permissible based on investigator judgment and local practice.	Do not resume tarlatamab until 7 days after the last seizure and after therapeutic levels of anti-seizure medication are likely to have been achieved.	If a second seizure occurs after resuming tarlatamab

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Abbreviations and footnotes defined on last page of table.

Table 6-2. Tarlatamab Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/Delay	Specific Management	Restart guidance	Permanent Discontinuation
Cytokine Release Syndrome (see Section 11.11.1 for additional guidance and grading scale details)					
1	Symptoms are not life threatening and require symptomatic treatment only • Fever[b]: ≥ 38°C • Hypotension: none • Hypoxia: none	No action required	Administer: • Symptomatic treatment (eg, paracetamol/acetaminophen) for fever • Consider a single dose of dexamethasone (or equivalent) ranging from 4 mg to 10 mg. Monitor: • CRS symptoms including temperature, blood pressure, and pulse oximetry • Fluid status, maintain IVF as needed • Consider Chest X-ray and obtaining appropriate cultures to rule out infection For subjects with rapid onset (< 4 hours from start of infusion), extensive co-morbidities or poor PS, strong suggestion to manage per grade 3 CRS guidance below and local institutional guidelines.	No additional guidance	No additional guidance

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Abbreviations and footnotes defined on last page of table.

Table 6-2. Tarlatamab Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/Delay	Specific Management	Restart guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 11.11.1 for additional guidance and grading scale details)					
2	• Fever[b]: ≥ 38°C WITH • Hypotension: not requiring vasopressors AND/OR[c] • Hypoxia: requiring low-flow nasal cannula[d] or blow-by	Delay tarlatamab until event improves to CRS grade ≤ 1.	Administer: • Symptomatic treatment (eg, paracetamol/acetaminophen) for fever • Consider a single dose of dexamethasone (or equivalent) ranging from 4 mg to 10 mg. • Supplemental oxygen when oxygen saturation is < 90% on room air (low-flow [≤ 6 L/minute] nasal cannula or blow-by) • Intravenous fluids when systolic blood pressure is < 85 mmHg. Persistent tachycardia (eg, > 120 bpm) may also indicate the need for intervention for hypotension. Monitor: • CRS symptoms including temperature, blood pressure, and pulse oximetry • Fluid status, maintain IVF as needed • Cardiac and other organ function • Consider Chest X-ray and obtaining appropriate cultures to rule out infection For subjects with rapid onset (< 4 hours from start of infusion), extensive co-morbidities or poor performance status, strong suggestion to manage per grade 3 CRS guidance below and local institutional guidelines.	The next infusion may be administered if the event has resolved to grade ≤ 1 prior to restarting treatment	If there is no improvement to CRS ≤ grade 1 within 7 days

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Abbreviations and footnotes defined on last page of table.

Table 6-2. Tarlatamab Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 11.11.1 for additional guidance and grading scale details)					
3	• Fever[b]: ≥ 38°C WITH • Hypotension: requiring a single vasopressor (excluding vasopressin) AND/OR[c] • Hypoxia: requiring high-flow nasal cannula[d], facemask, nonrebreather mask, or Venturi mask	Delay tarlatamab until event improves to CRS grade ≤ 1.	Administer: • Symptomatic treatment (eg, paracetamol/acetaminophen) for fever • Supplemental oxygen (high-flow nasal cannula [> 6 L/min]), facemask, non-rebreather mask, or Venturi mask), as needed • A vasopressor ± vasopressin, as needed • Dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/d). The dose should then be reduced step-wise. AND/OR • Consider use of tocilizumab (in countries where available) as an additional therapy in this setting at a dose of 4-8 mg/kg as a single dose. Tocilizumab can be repeated for an additional 3 doses with at least an 8-hour interval between doses. • If tocilizumab is not available, siltuximab (an anti-IL-6 monoclonal antibody) may be used in the management of CRS, following the criteria outlined in this table. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an IV infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (Sylvant Prescribing Information), and the CARTOX Working Group Guidelines for CRS management (Neelapu et al, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of tarlatamab. Siltuximab may not be repeated in an individual subject who develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab. • As per local institutional guidelines.	The next infusion may be administered if all of the following criteria are met: • The Amgen medical monitor must be consulted prior to resuming treatment • The event has resolved to grade ≤ 1 prior to resuming treatment In case of infusion interruption, continue treatment with next scheduled infusion. Do not resume prior infusion or administer delayed infusion.	If there is no improvement to CRS ≤ grade 2 within 5 days and CRS ≤ grade 1 within 7 days. OR If CRS grade 3 occurs at the step dose. OR In the case of 2 separate grade 3 CRS events.

Abbreviations and footnotes defined on last page of table.

Table 6-2. Tarlatamab Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/Delay	Specific Management	Restart guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 11.11.1 for additional guidance and grading scale details)					
3 (cont)			Monitor: • CRS symptoms including temperature, blood pressure, and pulse oximetry • Fluid status, maintain IVF as needed • Consider chest X-ray and obtaining appropriate cultures to rule out infection • If refractory hypotension (after 2 fluid boluses), consider ECHO Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines		
4	Life-threatening symptoms • Fever[b]: ≥ 38°C WITH • Hypotension: requiring multiple vasopressors (excluding vasopressin) AND/OR[c] • Hypoxia: requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Immediately stop any ongoing infusion	Administer: • Symptomatic treatment (eg, paracetamol/acetaminophen) for fever • Supplemental oxygen (positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation), as needed • Multiple vasopressors, as needed • Dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/d). Further corticosteroid use should be discussed with the Amgen medical monitor. • Tocilizumab should be administered at a dose of 4-8 mg/kg as a single dose. Tocilizumab can be repeated for an additional 3 doses with at least an 8 hour interval between doses	Do not resume tarlatamab.	Permanently discontinue tarlatamab

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Abbreviations and footnotes defined on last page of table.

Table 6-2. Tarlatamab Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/Delay	Specific Management	Restart guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 11.11.1 for additional guidance and grading scale details)					
4 (cont)			• If tocilizumab is not available, siltuximab (an anti-IL-6 monoclonal antibody) may be used in the management of CRS, following the criteria outlined in this table. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an IV infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (Sylvant Prescribing Information), and the CARTOX Working Group Guidelines for CRS management (Neelapu et al, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of tarlatamab. Siltuximab may not be repeated in an individual subject who develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab. Monitor: • CRS symptoms including temperature, blood pressure, and pulse oximetry • Fluid status, maintain IVF as needed • Consider chest X-ray and obtaining appropriate cultures to rule out infection • If refractory hypotension (after 2 fluid boluses), consider ECHO Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines.		

Abbreviations and footnotes defined on last page of table.

Table 6-2. Tarlatamab Dose Modification Guidelines for Adverse Events

Grade	Interruption/Delay	Specific Management	Restart guidance	Permanent Discontinuation
Tumor Lysis Syndrome (TLS) – Grading according to Common Terminology Criteria for Adverse Events (CTCAE v.5.0) (see Section 11.11.3)				
Present	Immediate interruption/delay until event has improved to grade ≤ 1	TLS should be managed according to the local SOC and institutional guidelines.	• Resume only if successfully managed and improvement to ≤ grade 1 in ≤ 14 days • Consult with Amgen medical monitor. • In case of infusion interruption, continue treatment with next schedule infusion, do not resume prior infusion or administer delayed infusion. • Monitoring: per Monitoring Guidance for first tarlatamab administration (Section 6.1.1)	If subject missed more than 2 consecutive doses of tarlatamab OR In case of repeat TLS event, or life-threatening TLS, permanently discontinue tarlatamab.

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Abbreviations and footnotes defined on last page of table.

Table 6-2. Tarlatamab Dose Modification Guidelines for Adverse Events

Grade	Interruption/Delay	Specific Management	Restart guidance	Permanent Discontinuation
Non-febrile Neutropenia				
3[e]	Delay 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 is permitted	Resume tarlatamab no less than 72 hours after the initial observation of the grade 3 adverse event	No additional guidance
4[e]	Delay 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	Initial grade 4 non-febrile neutropenia event lasts > 7 days OR Grade 4 event reoccurs

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Abbreviations and footnotes defined on last page of table.

Table 6-2. Tarlatamab Dose Modification Guidelines for Adverse Events

Pituitary Gland Dysfunction (Gonzalez-Rodriguez and Rodriguez-Abreu, 2016)
• Monitor for signs and symptoms of pituitary gland dysfunction. Consider the following studies as indicated: TSH, FSH, LH, cortisol, FT4, testosterone/estradiol ACTH, prolactin, and IGF-1 – Abnormal hormone monitoring result or clinical suspicion of pituitary gland dysfunction (headache, fatigue, asthenia, impaired vision, vomiting, hypotension, amenorrhea, impotence) – Diagnostic tests: brain MRI (if clinically indicated), blood pressure, glycemia, plasma and urine osmolarity, electrolytes, laboratory values (ACTH, TSH, FSH, LH, IGF-1, plasma cortisol, FT4, prolactin, testosterone/estradiol) • Urgent endocrinology consultation • Once pituitary gland dysfunction is confirmed, delay scheduled dose of tarlatamab • Once residual related toxicity ≤ grade 2, clinically stable on replacement therapy, and < 10 mg prednisone or equivalent, resume tarlatamab • Continue endocrinological surveillance
Hepatotoxicity
For Stopping and Rechallenge Rules please refer to Section 11.7.

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ACTH = adrenocorticotropic hormone; BiPAP = bi-level positive airway pressure; CARTOX = CAR-T-cell-therapy-associated TOXicity; CRS = cytokine release syndrome; CPAP = continuous positive airway pressure; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; EOT = end of treatment; FSH = follicle-stimulating hormone; FT4 = free T4; G-CSF = granulocyte colony-stimulating factor; GI = gastrointestinal; ICANS = immune effector cell-associated neurologic syndrome; ICU = intensive care unit; IGF-1 = insulin-like growth factor 1; IL-6 = interleukin 6; IV = intravenous; IVF = intravenous fluid(s); LH = luteinizing hormone; MRI = magnetic resonance imaging; N/A = not applicable; NSAIDS = non-steroidal anti-inflammatory drugs; OR = objective response; PS = performance status; Q2 = every 2; RT-PCR = real time polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; TLS = tumor lysis syndrome; TSH = thyroid-stimulating hormone

[a] American Society for Transplantation and Cellular Therapy (ASTCT) grading system for CRS (Lee et al, 2019).

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In subjects who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab, siltuximab, or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[c] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[d] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

[e] For neutropenia adverse events grade ≤ 2, please follow institutional guidelines for management.

[f] Based on Immune Effector Cell Therapy Toxicity Assessment and Management (also known as CARTOX) https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf

[g] Per CTCAE 5.0

For all other treatment interruptions or delays, re-start tarlatamab in accordance with the following guidelines in Table 6-3:

Table 6-3. Step-dose Rechallenge Requirement After Tarlatamab Delay

Last Dose Administered	Duration of Delay from the Last Dose Administered	Action
Step dose (1 mg)	≤ 14 days	Proceed with tarlatamab target dose and then continue treatment **regimen**
	> 14 days	Repeat tarlatamab step dose per cycle 1 guidelines, including pre-medication and monitoring requirements (Refer to Table 6-1).
First target dose (10 mg)	≤ 21 days	Proceed with tarlatamab target dose and then continue treatment Q2W
	> 21 days	Repeat tarlatamab step dose schedule per cycle 1 guidelines, including pre-medication and monitoring requirements (Refer to Table 6-1).
Any subsequent target dose (10 mg)	≤ 28 days	Proceed with tarlatamab target dose and then continue treatment Q2W
	> 28 days	Repeat tarlatamab step dose per cycle 1 guidelines, including pre-medication and monitoring requirements (Refer to Table 6-1).

Q2W = every 2 weeks.

6.2.2.2 Non-Amgen Noninvestigational Product/Auxiliary Medicinal Product (SOC Chemotherapy) - Lurbinectedin, Topotecan, or Amrubicin

The reason for lurbinectedin, topotecan, or amrubicin delay or discontinuation is to be recorded on each subject's CRF. Refer to the regional prescribing information or institutional guidelines (if not addressed in prescribing information) for recommended dose modifications.

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 and non-investigational products(s)/auxiliary medicinal product(s) will be provided to the site.

6.4 Method of Treatment Assignment

Subjects will be randomized in a 1:1 allocation ratio, to receive tarlatamab or SOC therapy (lurbinectedin or topotecan in US, Canada, Australia, Singapore, Korea; amrubicin in Japan; or topotecan in all countries except Japan), respectively, in an open-label manner. For subjects randomized to the SOC arm in US, Canada, Australia, Singapore, and Korea, lurbinectedin or topotecan may be selected for treatment based on investigator discretion.

The stratification factors are:

- Prior anti-PD-(L)1 exposure (yes vs no)
- Chemotherapy-free interval (≥ 180 days, < 180 to ≥ 90 days, or < 90 days)
- Presence (previous or current) of brain metastases (yes or no)
- Standard of care (topotecan/amrubicin vs lurbinectedin)

The randomization will be performed by IRT, and the randomization number will be provided to the site via IRT. The randomization date is to be documented in the subject's medical record and on the Subject Enrollment CRF (via IRT).

6.5 Blinding

To maintain trial integrity in this open-label study, post-baseline data analyses of primary and key secondary endpoints will not be produced or reviewed by the study team prior to interim/primary analysis snapshot analysis.

6.6 Treatment Compliance

When subjects are dosed at the site, they will receive study treatment 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 on the CRF.

When subjects self-administer oral topotecan at home, compliance with the treatment will be assessed through a web-based diary and documented in the source documents and CRF. The web-based diary **should** be completed daily with the response 'Yes' (if oral topotecan is taken) or 'No' (if oral topotecan has not been taken, in the event of dose interruption due to adverse event, etc,).

6.7 Treatment of Overdose

The effects of overdose of tarlatamab are not known. For overdose information on SOC chemotherapy, please refer to the regional prescribing information or institutional guidelines (if not addressed in prescribing information) for recommended treatment for overdose.

The administered tarlatamab 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 **(refer to Section 11.4, Appendix 4).**

A dose of ≥ 10% higher than the intended tarlatamab dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event".

6.8 Prior and Concomitant Treatment

6.8.1 Prior Treatment

Prior therapies (including prescription and non-prescription, herbal, and alternative therapies) that were being taken/used from 21 days prior to first dose of study treatment

through the end of SFU period will be collected. Antibiotic therapy for the previous 3 months from first dose of study treatment will also 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.

Prior therapies taken for SCLC dating back to initial diagnosis will be collected. For all prior therapies taken for SCLC (eg, chemotherapy, immunotherapy, biological therapy, or targeted therapy), the following information should be collected (in the order they were administered):

- therapy name
- indication
- dose and schedule of the agent(s)
- unit
- frequency
- start and stop dates
- best response
- **best response date**
- disease stage in which it was administered
- reason for discontinuation (disease progression, clinical progression, toxicity, subject's decision, completion of treatment)
- **date of progression**

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.

6.8.2 Concomitant Treatment

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

Concomitant therapies (including prescription and non-prescription, herbal, and alternative therapies) are to be collected from main study informed consent through the end of SFU period. **Start and stop time should also be recorded for therapies taken for CRS and ICANS.**

For anticancer therapies consisting of multiple individual components, information for each component should be collected. For other (not taken for the disease under study)

concomitant therapies (including vaccines), collect therapy name, indication, dose, unit, frequency, start and stop dates.

Vaccines

Every effort should be made to complete any planned vaccinations prior to study treatment. Refer to Section 5.2 for details and restrictions prior to first dose of study treatment. The use of vaccines (except live and live-attenuated vaccines) may be allowed during study treatment (refer to Section 6.1.6 for details). In the event where a patient requires steroids for treatment of adverse events, vaccination should be avoided while on steroids.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Subjects have the right to withdraw from investigational product and/or non-investigational products(s)/auxiliary medicinal product(s), protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or noninvestigational products(s)/auxiliary medicinal product(s), protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 7.1 and Section 7.2.1.

7.1 Discontinuation of Study Treatment

Subjects (or a legally authorized representative) can decline to continue receiving investigational product and/or noninvestigational products(s)/auxiliary medicinal product(s) 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 noninvestigational products(s)/auxiliary medicinal product(s) and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 1.3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and product complaints (including device-related adverse events, as applicable) and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or noninvestigational products(s)/auxiliary medicinal product(s) 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**. At minimal vital status (survival status) should be collected, through as an example, direct or family member contact or family members contact or through the attending physician or medical records, public registries, and public records, subject to local laws and regulations**.

Reasons for early removal from protocol-required investigational product(s), non-investigational products(s)/auxiliary medicinal 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
- disease progression
- requirement for alternative therapy
- pregnancy

7.2 Subject Discontinuation/Withdrawal From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. **The subject is not considered to have ended the study until there is no means to continue collection of vital status (survival status).** 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. Subjects who are withdrawn or removed from treatment or the study will not be replaced.

If a subject withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see

Section 11.6 for further details). Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if 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 **at risk to be** lost to follow-up, where permitted per local regulation, the investigator or designee must make every effort to regain contact with the subject.
- **The investigator or designee should attempt** 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods [contact the patient's family or direct assigned contact]). These contact attempts are to be documented in the subject's medical record.
- **The investigator should contact the subject's attending physician.**
- If the subject continues to be unreachable **or vital status (survival status) cannot be obtained through any of the above actions**, they 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 **vital status (**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 (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 (Section 1.3), is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

Screening:

The main study informed consent must be obtained before completing any screening procedure with the following exceptions:

- assessments that were performed as SOC prior to signature of informed consent, but within the protocol specified window (a maximum of 21 days prior to randomization) can be used as screening assessments and do not need to be repeated to confirm subject eligibility
- discontinuation of standard therapy for any disallowed therapy

After the subject has signed the main ICF, the site will register the subject as screened in the IRT in order to assess eligibility for participation. The screening window (including randomization in IRT for eligible subjects) is up to 21 days from the date of signing the main study informed consent.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria prior to randomization. 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 5.5) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period **and prior to randomization**, the subject will be registered in IRT as a screen fail. Screen fail subjects may be eligible for rescreening up to 2 times at the discretion of the investigator, after consultation with the Amgen Medical Monitor.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 21-day screening window will begin. Subjects will retain the same subject identification number previously assigned. Subjects rescreening within 21 days of the signing of the original main study informed consent need to repeat the assessment(s) that did not originally meet the eligibility criteria and ensure all other eligibility criteria are still met prior to enrollment and study assessments are still valid and within the screening window (ie,

imaging scans, local labs, etc,). If the rescreening period begins more than 21 days after the original signing of the main study ICF, all screening procedures (except the 3 exceptions mentioned above), including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 1.3). For tarlatamab, on-study cycle 1 visits may be completed within ± 1 day, cycle 2 visits have a ± 2-day window, and all subsequent visits beginning in cycle 3 will have a ± 3-day window, unless otherwise specified (Note: the treatment window for SOC therapies is based on regional prescribing information). Day 1 should occur on the day of randomization wherever possible, however day 1 can occur up to end of the third calendar day from randomization, if needed, due to logistical reasons. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) is to be administered last during each visit that it is required.

8.1.3 End of Treatment

Upon permanent discontinuation from study treatment for any reason, an End of Treatment (EOT) visit will be performed as soon as possible (within 14 days) after last dose and prior to start of subsequent anti-cancer therapy. **If a subject is unable to attend the EOT visit, the subject at minimum should be followed via telephone, clinic visit, or chart review to assess for survival and the commencement of subsequent cancer therapy.**

8.1.4 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, an SFU visit will be performed approximately **60** (+ 5) days after the last dose of study treatment, even if subsequent anti-cancer therapy has been initiated within that period. **If a subject is unable to attend the SFU visit, the subject at minimum should be followed via telephone, clinic visit, or chart review to assess for survival and the commencement of subsequent cancer therapy.**

8.1.5 Long-term Follow-up

Following the SFU visit, there will be an LTFU period for clinical evaluation of disease status and survival. Subjects will be followed via telephone, clinic visit, or chart review to assess for survival and/or the commencement of subsequent cancer therapy every 12 weeks (± 14 days) from the SFU visit (or last imaging visit, whichever is later) for up

to 3 years after the last subject is enrolled, or 1 year from the subject's last dose of study treatment, whichever is later.

Vital status (survival status), imaging and tumor assessment (until radiographic disease progression), subsequent anticancer treatment (ie, subsequent therapies taken for SCLC), serious adverse events suspected to be related to study treatment, and urine pregnancy test **60** days after last dose of tarlatamab will be collected.

The assessments that will be collected during the LTFU are designated in the Schedule of Activities (Section 1.3).

8.1.6 End of Study

Refer to Section 4.5 for the end of study definition. The end of study visit is the last visit shown in the Schedule of Activities (Section 1.3) which is the final LTFU visit.

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 other study-specific procedures are performed. A subject is considered to have entered the study at the time of signing the main study informed consent.

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 tarlatamab.

8.2.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started within 5 years prior to randomization through the time of first dose of study treatment. Medical history will include information on the subject's concurrent medical conditions. The current toxicity grade will be collected for each condition that has not resolved.

In addition to the medical history above, SCLC history must date back to the initial diagnosis. **For patients with no exposure to prior anti-PD-(L)1, the reason for nonuse will be collected.**

8.2.4 Physical Examination

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

Neurological Examination

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.

8.2.5 Physical Measurements

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

8.2.6 Substance Use History

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

8.2.7 Performance Status

The subject's PS will be assessed using the ECOG performance scale (see Section 11.9).

8.3 Efficacy Assessments

8.3.1 Radiological Imaging Assessment

The extent of disease will be evaluated by contrast-enhanced computed tomography (CT)/magnetic resonance imaging (MRI) according to RECIST 1.1 (Section 11.10). All radiological imaging will be performed as indicated in the Site Imaging Manual provided by the central imaging core laboratory. In order to reduce radiation exposure for subjects, low dose CT should be utilized whenever possible. All scans will have a ± **7**-day window.

Screening scans:

The screening scans must be performed within the 21-day screening period. If there are multiple screening scans, the 1 closest to the enrollment will be used as baseline.

Assessments that were performed as SOC prior to signature of informed consent, but within the 21-day screening period can be used as screening assessments and do not need to be repeated to confirm subject eligibility.

Radiological assessment must include CT/MRI of the chest, abdomen, and pelvis, as well as assessment of all other known sites of disease (as detailed within the Site Imaging Manual).

All subjects must have CT/MRI of the brain performed within the 21-day screening period. All brain scans for subjects are required to be MRI unless MRI is not possible, in which case CT with contrast is acceptable.

Subsequent scans:

Every effort should be made to perform all subsequent scans in the same manner (eg, with the same contrast, MRI field strength) as at screening, preferably on the same scanner.

Subsequent brain CT/MRI scans may be performed at any time, if in the judgement of the managing physician, the subject displays signs, or symptoms of CNS metastasis.

During treatment and follow-up, radiological imaging of the chest, abdomen, pelvis, as well as all other known sites of disease (including brain), will be performed independent of treatment cycle and regardless of dose delays as specified in the Schedule of Activities (Section 1.3). Imaging may also be performed more frequently if clinically necessitated at the discretion of the managing physician. Confirmed radiographic response (CR, PR) requires confirmation by a repeat scan at least 4 weeks after the first documentation of response but may be performed later at the next scheduled scan, see Section 11.10. Radiologic imaging and tumor assessment will be performed until radiographic progression, withdrawal of consent, death, or end of study, whichever occurs first.

Following documented radiographic progression, the subject may remain on study treatment provided certain criteria are met, see Section 6.1.7.

Detailed information regarding submission of images to the central imaging core laboratory is found in the Site Imaging Manual.

8.3.2 Clinical Outcome Assessments

Clinical outcome assessments should be collected as indicated in the Schedule of Activities (Section 1.3) and should be collected independent of treatment cycle and

regardless of dose delays. If an assessment is not performed as indicated, the reason for a missing assessment (prespecified reasons) should be reported.

8.3.2.1 EORTC-QLQ-C30 and EORTC-QLQ-LC13

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC-QLQ-C30) was developed to assess the quality of life in cancer subjects across tumor types. The QLQ-C30 has been tested and validated with multiple myeloma subjects (Petrucci et al, 2013; Kvam et al, 2011; Wisløff et al, 1996) and has also been used in NSCLC (Aaronson et al, 1993; Niezgoda and Pater, 1993). It is a self-reporting 30-item generic instrument which assesses 5 functional domains (physical, role, emotional, cognitive, social), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a global health status/QOL scale (Aaronson et al, 1993).

The EORTC-QLQ-LC13 is a disease-specific supplement to the EORTC-QLQ-C30 (Ahmedzai et al, 1994). The lung cancer questionnaire module comprises both multi-item and single-item measures of lung cancer-associated symptoms (ie, coughing, hemoptysis, dyspnea, and pain) and side-effects from conventional chemo- and radiotherapy (ie, hair loss, neuropathy, sore mouth, and dysphagia).

8.3.2.2 PRO-CTCAE

Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a 78-item library used to measure patient-reported symptomatic adverse events. Users can select items those are most relevant to disease, treatment profile, and fit for purpose to document patients' experience. Each symptom can be rated by up to 3 attributes, presence/frequency, severity, and/or interference of the adverse event. Based on the safety profile of tarlatamab, the study included the following symptoms of taste changes, shivering or shaking chills, anxiety, constipation, vomiting, headache, concentration, rash, palpitations, arm or leg swelling, nausea, dizziness, bruising, fatigue, and decreased appetite which are deemed relevant for site of cancer as well as cancer treatment.

8.3.2.3 FACT-G

The Functional Assessment of Cancer Therapy - General (FACT-G) is a 27-item questionnaire designed to measure 4 domains of health-related quality of life in cancer patients: physical, social, emotional, and functional well-being.

The GP5 of the FACT-G is a single item “I am bothered by side effects of treatment” rated on a 5-point Likert scale from “not at all” to “very much” is an item included in the Physical Well-Being subscale of the PRO assessment instrument FACT-G. It has been evaluated and validated as a useful summary index of side effect impact or burden to the individual subject (Pearman et al, 2018).

8.3.2.4 EQ5D-5L

The 5-Level EuroQol 5-Dimension (EQ5D-5L) questionnaire is a 2-page, standardized instrument for use as a measure of health outcome developed by the EuroQol group (Rabin and de Charro, 2001). It is comprised of a 5-dimension health status measure and a visual analogue scale (VAS). The 5-dimension health status measure evaluates: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression based on a 5-level scale: no problems, slight problems, moderate problems, severe problems, an extreme problem. The VAS records the subject's self-rated health on a vertical, VAS where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. The EQ5D-5L takes about 3 minutes to complete.

8.3.2.5 Patient Global Impression of Change and Patient Global Impression of Severity

Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) are anchor measures used in measurement of within-patient meaningful change (response) thresholds for disease symptoms/impacts of interest. PGIC scale asks respondents to rate the overall change in symptoms, overall status, etc, since initiating treatment with the medication. The 5-level PGIC response options are ‘much better’, ‘a little better’, ‘about the same, ‘a little worse’, and ‘much worse’. PGIS scale asks respondents to describe the severity of their symptoms, overall status, etc, over the past week. The 4-level PGIS response options are ‘none’, ‘mild’, ‘moderate’, and ‘severe’.

8.3.2.6 Brief Pain Inventory - Short Form (BPI-SF [Pain])

The BPI-SF (Pain) is a valid and reliable instrument, which is a commonly used tool to capture severity of pain and its impact on the daily functioning. The BPI-SF measures intensity of pain at 4 time point (worst, least, average, and right now), pain relief, and 7 interference items (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life). Scoring for pain ranges from 0 (no pain) to 10 (worst pain) and likewise for pain interference from 0 (no interference) to 10 (complete interference).

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

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

For subjects receiving tarlatamab, vital signs collected during the first 2 doses (on study treatment infusion days; see Section 1.3) will be assessed accordingly during the following time points:

Table 8-1. Vital Signs and Pulse Oximetry

All subjects receiving tarlatamab	
Cycle 1	
Day 1 and day 8	• Pre-infusion, end of infusion, and 60 (± 5) minutes after end of infusion (EOI)
For subjects that require monitoring for restarting due to delays between doses (refer to Table 6-1); collect vital signs according to the timepoints in cycle 1 day 1 and day 8 guidance. Vital signs thereafter will be collected **predose** as indicated in the Schedule of assessments (see Section 1.3), including scheduled visits on cycle 1 day 2 and cycle 1 day 9.	

For subjects receiving lurbinectedin, topotecan, or amrubicin, vital signs will be collected prior to administration at the visits indicated in the Schedule of Activities (see Section 1.3).

8.4.2 Electrocardiograms

Electrocardiograms (ECGs) will be performed as indicated in the Schedule of Activities (see Section 1.3).

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, corrected QT interval (QTc), and PR intervals.

The 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.

8.4.3 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 Events 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).

8.4.4 Vital Status (Survival Status)

Vital status (survival status) must be obtained for all subjects within the limits of local law **(see Section 7.1 and Section 7.2)**. 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.

8.4.5 Other Safety

8.4.5.1 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 Assessments (see Section 1.3). Echocardiogram/MUGA should include an evaluation from left ventricular ejection fraction (LVEF). Additional ECHO/MUGA assessments may be performed as clinically indicated.

8.4.5.2 Cytokine Release Syndrome (CRS)

Cytokine release syndrome is defined a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end organ dysfunction.

Refer to Section 11.11.1 for details on specific guidance for CRS.

8.4.5.3 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

For this trial, 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 11.11.2 for details on specific guidance for ICANS.

8.4.5.4 Hepatitis B

Subjects with resolved HBV infection, defined as absence of HBsAg and presence of antibody to anti-HBc; and subjects with chronic HBV infection inactive carrier state, defined as presence of HBsAg and HBV DNA viral load below the limit of quantification

(HBV DNA negative) should undergo consultation with a specialist in HBV and have HBV DNA testing and monitoring of HBV DNA every 12 weeks (± 2 weeks) or more frequently, if clinically indicated, through safety follow-up.

Subjects who are chronic HBV infection inactive carriers should be considered for HBV reactivation prophylaxis treatment as per a specialist in hepatitis B following local or institutional practice guidelines. Subjects with resolved hepatitis B are at lower risk of HBV reactivation with anti-cancer therapies, however, they should also be potentially considered for HBV prophylaxis as per a HBV specialist following local or institutional guidelines.

Any subject who becomes HBV DNA positive or develops reactivation of HBV will have study treatment interrupted and receive appropriate antiviral treatment as per a specialist in hepatitis B. Resumption of clinical study therapy may be considered in subjects whose HBV reactivation is controlled and where the benefits of clinical study therapy outweigh the risks. After cessation of study therapy for any reason, any ongoing monitoring and antiviral treatment should be under the guidance of a specialist in HBV. Subjects that have received hepatitis B vaccination with only anti-HBs Ab positivity and no clinical signs of hepatitis do not require HBV DNA monitoring.

8.4.5.5 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.

8.4.6 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4 **with the following exceptions: CRS and ICANS will be graded according to American Society for Transplantation and Cellular Therapy (Lee et al, 2019) as described in Table 6-2 and Section 11.11.**

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

8.4.6.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE v5.0 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 product(s) or noninvestigational product(s)/auxiliary medicinal product(s) through the SFU visit or **60** days after the last dose of investigational product(s) or non-investigational product(s)/auxiliary medicinal product(s), whichever is later, are reported using the Events CRF.

8.4.6.1.2 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 SFU visit or **60** days after the last dose of investigational product(s) or noninvestigational product(s)/auxiliary medicinal product(s), whichever occurs later, are reported using the Events CRF.

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

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

8.4.6.1.3 Serious Adverse Events After the Protocol Required Reporting Period

During the LTFU period, if the investigator becomes aware of serious adverse events suspected to be related to the investigational product after the protocol-required reporting period (as defined in Section 8.4.6.1.2 is complete, 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 following 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, then these serious adverse events will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the event.

Serious adverse events reported after the end of the study will be captured within the safety database as clinical **study** cases and handled accordingly based on relationship to investigational product.

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

8.4.6.2 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 due to the method of inquiry. Open-ended and non-leading verbal questioning of the subject is the preferred method to collect information about adverse event occurrence.

8.4.6.3 Follow-up of Adverse Events and Serious Adverse Events

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

All new information for previously reported serious adverse events must be sent to Amgen immediately and no later than 24 hours following 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.

8.4.6.4 Regulatory Reporting Requirements for Safety Information

If subject is permanently withdrawn from investigational product(s), and/or non-investigational product(s)/auxiliary medicinal product(s) because of a serious adverse event, this information must be submitted to Amgen.

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

The sponsor 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 for suspected unexpected serious adverse reactions **(SUSARs) will be reported by the sponsor** according to local regulatory requirements **(eg, electronic submission to the Eudravigilance database in the EU as per EU Clinical Trial Regulation 536/2014) as well as** sponsor policy and forwarded to investigators as necessary.

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

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with 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.

8.4.6.5 Safety Monitoring Plan

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

8.4.6.6 Other Safety Findings/Special Situations

All medication errors, misuse or abuse of the investigational product when associated with a serious adverse event must be reported to Amgen or designee immediately and no later than 24 hours of the investigator's awareness by collecting and recording the Other Safety Findings (OSF)/Special Situations (SS) event on the Clinical Trial electronic serious adverse events Contingency Report Form and submitting the form to Amgen Global Patient Safety or designee. Further details and definitions regarding OSF/SS - medication errors, misuse, or abuse, can be found in Section 11.4.

8.4.6.7 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 **60** days and **60** days, respectively, after the last dose of tarlatamab (Note: details of pregnancies and/or breastfeeding requirements for SOC therapies are based on regional prescribing information).

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, and ectopic pregnancy) are considered serious adverse events.

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

Pregnancy Testing

A serum pregnancy test should be completed at screening within 7 days of C1D1 and serum or urine test completed on day 1 of each cycle, at EOT, and at SFU for females of childbearing potential (Section 1.3). During study treatment, all pregnancy tests completed at day 1 of each cycle need to be performed and reviewed before treatment administration. During LTFU, additional pregnancy testing should be performed **60** days after last dose of tarlatamab (Section 1.3). For subjects receiving SOC, refer to the regional prescribing information and/or local guidelines.

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

Additional 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 randomized to tarlatamab will have PK samples assessed.

Blood samples will be collected for measurement of serum concentrations of study treatment as specified in **Section 1.3**. Blood must not be drawn from a port catheter during investigational product infusion and must be collected within 30 minutes after end of infusion prior to PK sample collection. If a permanent central line with more than 1 lumen is used, blood draws can be done via the lumen that is not used for drug administration. However, the preference is for PK samples to be drawn peripherally. The actual date and time (24-hour clock time) of each sample will be recorded.

8.7 Antibody Testing Procedures

All subjects randomized to tarlatamab will have blood samples collected for antibody testing.

Blood sample(s) for antibody testing are to be collected according to the time points specified in **Section 1.3** for the measurement of anti-tarlatamab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies.

Refer to the Schedule of Activities (Section 1.3), as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions. More frequent antibody testing or testing for a longer period of time may be requested in the event of safety-related concerns.

8.8 Biomarkers

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

8.8.1 Biomarker Assessment During the Study

Tumor Tissue

[redacted]

Blocks are preferred, if available, but in lieu of blocks, unstained slides **can be submitted**. Block return may not be possible in every country. The tumor specimen submitted should be of sufficient quantity to allow for immunohistochemistry, DNA, and transcriptional analysis and include the corresponding pathology report; see the laboratory manual for details.

At end of treatment, fresh tissue samples will be collected after informed consent. These samples should be obtained following local standard practice that pose minimal risk to the patient (including investigator assessment of subject condition to undergo biopsy procedure).

[redacted].

When permitted by local regulations, blood and tumor tissue samples are to be collected and assessed for at the time points specified in the Schedule of Activities (Section 1.3):

Blood Samples

8.8.1.1 Biomarker Development

Samples will also be collected to develop or address biomarker hypotheses related to tarlatamab activity. These samples will also be used for developing methods that enable better understanding of the disease.

8.8.1.2 Biomarker Future Research

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

If consent is provided by subjects, any remaining samples collected at the time points specified in the Schedule of Activities (Section 1.3), including samples collected for

biomarker assessments may be used for future research as described in Section 11.6. No additional samples will be collected for future research.

Amgen or another third-party manufacturer may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to tarlatamab or non-investigational product(s)/auxiliary medicinal product(s) to investigate and further understand SCLC.

8.9 Medical Resource Utilization and Health Economics

Medical Encounters

Medical resource utilization data, associated with medical encounters will be collected on the CRF by the investigator and study-site personnel for all subjects throughout the study. protocol-required procedures, tests, and encounters are excluded from the analysis of medical resource utilization and health economics.

The data collected may be used to conduct medical resource use analyses and will include:

- Number and duration of hospitalization (total days or length of stay, including duration by wards eg, intensive care unit)
- Number and type of diagnostic and therapeutic tests and surgical and nonsurgical procedures
- Reason for hospitalization (eg, adverse event such as CRS/ICANs or other)

Cytokine Release Syndrome

Medical resource utilization and health economics data, related to CRS, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. protocol-required procedures, tests, and encounters are excluded from the analysis of health resource utilization and health economics.

The data collected may be used to conduct economic analyses and may include hospitalizations (by ward), concomitant medications, diagnostic and therapeutic tests and procedures related to CRS.

9. Statistical Considerations

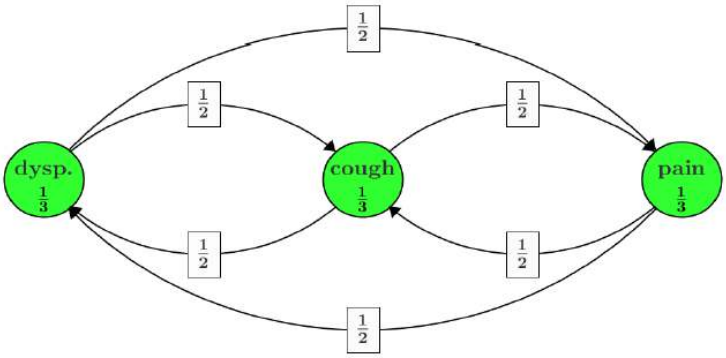
9.1 Statistical Hypotheses

The hypotheses of the primary efficacy endpoint OS, key secondary efficacy endpoint PFS, and key secondary PRO endpoints will be tested. The OS endpoint will be tested with [redacted] overall type I error (alpha) of [redacted] If OS is significant, the key secondary

efficacy endpoints of PFS and selected PRO endpoints can be tested sequentially in this order.

If both hypotheses of OS and PFS are rejected, the next 3 endpoints of change from baseline over time to week [redacted] in 3 lung cancer symptoms including chest pain, cough, and dyspnea will be tested using Holm's procedure as illustrated in Figure 9-1. Hypotheses are rejected sequentially based on the smallest p-value.

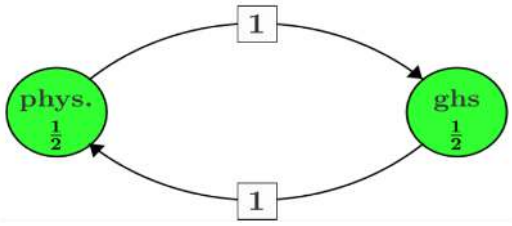
Figure 9-1. Holm's Procedure for Change from Baseline Over Time to Week [redacted] in 3 Lung Cancer Symptoms



dysp = dyspnea; pain = chest pain

If all 3 hypotheses listed above are rejected, the next 2 PRO endpoints will be tested using the Holm's procedure as illustrated in Figure 9-2, including change from baseline over time to week [redacted] in physical functioning and global health status. Hypotheses are rejected sequentially based on the smallest p-value.

Figure 9-2. Holm's Procedure for Change from Baseline Over Time to Week [redacted] in Physical Functioning and Global Health Status



phys = physical functioning; ghs=global health status

9.2 Sample Size Determination

Approximately [redacted] subjects per arm, total of approximately [redacted] subjects will be enrolled.

Overall Survival:

A total of [redacted] OS events will provide [redacted]% power to demonstrate superiority at an alternative HR of [redacted] with log-rank test using [redacted] overall type I error of [redacted] in a group sequential design with [redacted] interim analysis and [redacted] primary OS analysis. Under exponential assumption, assuming that the SOC mOS is [redacted] months (Spigel et al, 2021), a HR of [redacted] reflects a [redacted]-month improvement in OS of the tarlatamab arm over SOC arm. The interim analysis is triggered at the time when [redacted]% ([redacted] OS events occur. The dropout rate is anticipated to be [redacted]% per year assuming an exponential distribution.

With an enrollment rate of [redacted] subjects per month and a [redacted]-month ramp-up period [redacted] subjects per month for the first [redacted] months), it is estimated that the OS interim and primary analyses occur at approximately [redacted] and [redacted] months respectively.

Progression-free Survival:

The analyses of PFS will occur once OS endpoints can claim statistical significance and will only be tested once.

9.3 Populations for Analysis

The following populations are defined:

Population	Description
ITT analysis set	All randomized subjects. All subjects will be analyzed according to the randomized treatment arm. The ITT analysis set will be used for primary and secondary efficacy endpoints, unless specified otherwise.
Safety analysis set	All subjects who take at least 1 dose of study treatment. Subjects will be analyzed according to the study treatment they actually received.

9.3.1 Covariates

Covariates may be incorporated in selected models of efficacy endpoints. In addition to the stratification factors for randomization, the following additional covariates may be included:

- region (North America and Europe vs rest of world)
- best response on last prior therapy
- age (< 65 years vs ≥ 65 years)
- sex (male vs female)
- race (white, black, Asian, other)
- liver metastasis at baseline

- disease stage at initial diagnosis
- smoking history
- baseline ECOG
- baseline LDH

9.3.2 Subgroups

In addition to the stratification factors for randomization, primary and selected secondary endpoints may be examined in the following subgroups to investigate the consistency of treatment effects:

- region (North America and Europe vs rest of world)
- age (< 65 years vs ≥ 65 years)
- sex (male vs female)
- race (white, black, Asian, other)

[redacted]. The analyses of biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoints.

9.4 Statistical Analyses

The SAP 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

A description of the interim analysis and primary analysis is listed in Table 9-1. An average accrual rate of [redacted] subjects per month with a [redacted]-month ramp-up period is assumed. Depending on the actual enrollment rate, the number and timing of interim analyses could be different from what is projected here.

Table 9-1. Purpose and Timing of the Planned Analyses

Timepoint	Adaptive Decision and Analysis Scope	Number of subjects or events	Timing
IA [redacted]% OS)	Efficacy/Safety	Total of [redacted] OS events from both tarlatamab and SOC arm (the study is fully enrolled)	[redacted] months
OS PA	Efficacy/Safety	Total of [redacted] OS events from both tarlatamab and SOC arm	[redacted] months

IA = interim analysis; ORR = objective response rate; OS = overall survival; PA = planned analysis; SOC = standard of care.

An independent (external to Amgen) DMC will review unblinded interim safety and efficacy data as per DMC charter. The safety interim assessment from this committee will be approximately every 6 months afterward. If any safety interim is within 2 months of the IA, they may be combined.

Additionally, Amgen Pharmacovigilance conducts ongoing safety monitoring of blinded data throughout the clinical study.

Interim Efficacy Rules:

The testing of OS at the interim and primary analyses is adjusted using the Lan-DeMets alpha spending function with an O'Brien-Fleming approach. Table 9-2 shows the efficacy boundaries, which if crossed will enable claiming of OS efficacy. Data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan with the expectation that outstanding data issues are resolved ahead of the lock to the extent possible. The data supporting the interim analysis will be locked to prevent further changes.

Table 9-2. Stopping Boundaries of OS

Analysis	Information Fraction	Cumulative Events	Alpha spending	p-value (primary inference)	HR boundary
Interim	[redacted]				
Primary					

HR = hazard ratio; OS = overall survival.

9.4.1.2 Primary Analysis

The timing for the Primary Analysis (PA) of OS will be event driven and will happen when approximately [redacted] OS events are reached cumulatively in the 2 treatment groups. If OS early success is achieved in the IA (interim efficacy boundary specified in Table 9-2 is crossed), the IA will serve the purpose of PA of OS.

If OS achieves statistical significance at the interim analysis, key secondary endpoints (PFS and PRO) will be tested.

Data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan with the expectation that outstanding data issues are resolved ahead of the lock to the extent possible. The data supporting the primary analysis will be locked to prevent further changes.

9.4.1.3 Final Analysis

The final analysis will occur when enrollment is complete and each subject completes the study, including LTFU. Data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan with the expectation that outstanding data issues are resolved ahead of the lock to the extent possible. The data supporting the final analysis will be locked to prevent further changes.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamics, and biomarker data. Descriptive statistics on continuous data will include means, medians, standard deviations**,** and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

The primary inferential comparisons of the OS primary endpoint between tarlatamab and SOC arms will be made using a stratified log-rank test controlling for the randomization stratification factors. The HR and its 95% CI will be estimated using a Cox proportional hazards model stratified by the randomization stratification factors. Stratum that is too small may be collapsed in the stratified log-rank analysis. The distribution of OS, including the median and quartiles and their corresponding 95% CIs will be characterized using the Kaplan-Meier method. Overall survival rates for selected landmarks (eg, 1 year and 2 years) will be reported with the 95% CI.

Progression free survival will be analyzed using the same approach as OS. The PFS rate at 1 year will be reported with the 95% CI.

The descriptive analysis of ORR will be provided using the Cochran-Mantel-Haenszel chi-square test controlling for the randomization stratification factors. An estimate of the common odds ratio (95% CI) will be provided as a measure of the relative treatment effect. The ORR will be calculated and the 95% CI will be estimated using the Clopper-Pearson Method.

The descriptive analysis of DOR will be provided using the same methods as OS.

The change from baseline over time to 18 weeks in symptoms of chest pain and cough will be measured by a single question from EORTC-QLQ-LC13 will be analyzed using generalized linear mixed model for repeated measures with cumulative logit link. The change from baseline over time to [redacted] weeks in symptoms of dyspnea will be measured by a multiple item dyspnea domain from EORTC-QLQ-C30 and EORTC-QLQ-LC13 Symptom Scores. The change from baseline over time to [redacted] weeks in physical functioning and global health status will be measured by QLQ-C30 Domain Scores. The inferential comparison will be made using a mixed model for repeated measurement (MMRM). Missing data for the MMRM will be handled under the assumption of missing at random (MAR). Further details of secondary endpoint testing will be described in the SAP.

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary inferential comparisons of the OS primary endpoint between tarlatamab and SOC arms will be made using a stratified log-rank test controlling for the randomization stratification factors, using the ITT analysis set. The HR and its 95% CI will be estimated using a Cox proportional hazards model stratified by the randomization stratification factors. Stratum that is too small may be collapsed in the stratified log-rank analysis. The distribution of OS, including the median and quartiles and their corresponding 95% CIs will be characterized using the Kaplan-Meier method. The OS rates for selected landmarks (eg, 1 year and 2 years) will be reported with the 95% CI.
Secondary	PFS will be analyzed using the same approach as OS. Further details of the censoring rules will be described in the SAP. The PFS rate at 1 year will be reported with the 95% CI. The descriptive analysis of ORR will use the Cochran-Mantel-Haenszel chi-square test controlling for the randomization stratification factors. An estimate of the common odds ratio (95% CI) will be provided as a measure of the relative treatment effect. ORR will be calculated and the 95% CI will be estimated using the Clopper-Pearson Method.

	The descriptive analysis of DOR will be provided using the same methods as OS. The change from baseline over time to 18 weeks in symptoms of chest pain and cough as measured by a single question from EORTC-QLQ-LC13 will be analyzed using generalized linear mixed model for repeated measures with cumulative logit link. The change from baseline over time to [redacted] weeks in symptoms of dyspnea as measured by a multiple item dyspnea domain from EORTC-QLQ-C30 and EORTC-QLQ-LC13 Symptom Scores, change from baseline over time to [redacted] weeks in physical functioning and global health status as measured by QLQ-C30 Domain Scores will be analyzed using a mixed model for repeated measurement (MMRM). Missing data for the MMRM will be handled under the assumption of missing at random (MAR).
Exploratory	Will be described in the SAP finalized before database lock

OR = objective response; ORR = objective response rate; PFS = progression free survival; SAP = statistical analysis plan; SOC = standard of care.

9.4.2.3 Safety Analyses

9.4.2.3.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Summary tables of the subject incidence of treatment-emergent adverse events, and grade ≥ 3, serious, treatment-related, and fatal treatment-emergent adverse events.

9.4.2.3.2 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics over time. Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated.

9.4.2.3.3 Vital Signs

The analyses of vital signs will include summary statistics over time. The incidence and percentage of abnormal changes in vital signs will be tabulated.

9.4.2.3.4 Physical Measurements

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

9.4.2.3.5 Electrocardiogram

The ECG measurements from this clinical study were performed as per SOC for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of single ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.4.2.3.6 Antibody Formation

The incidence and percentage of subjects who develop anti-tarlatamab antibodies at any time will be tabulated.

9.4.2.3.7 Exposure to Investigational Product

The number of cycles, duration, the cumulative dose, and the average dose of investigational product administered will be summarized.

9.4.2.3.8 Exposure to Non-investigational Product(s)/Auxiliary Medicinal Product(s)

Descriptive statistics will be produced to describe the exposure to noninvestigational product(s)/auxiliary medicinal product(s).

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 Drug dictionary.

9.4.2.4 Other Analyses

Pharmacokinetic data from this study may be pooled with other studies and may be analyzed using a population PK approach. The observed PK parameter values from non-compartmental analysis will be utilized to drive the qualitative (graphical) and quantitative relationship of tarlatamab exposures with relevant efficacy and or safety variables. The efficacy variables will be aligned with primary and key secondary endpoints. Relevant covariates may also be explored to assess the impact on exposure-response relationships. The selection of safety variables will be primarily driven by frequency of events and clinical relevance. Additional pharmacodynamic variables may also be explored if deemed clinically relevant. These analyses will not be part of the clinical study report.

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASR	Annual Safety Report
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BIL	Bilirubin
BiTE	Bispecific T cell Engager
BOR	best overall response
BPI-SF	Brief Pain Inventory - Short Form
BSA	body surface area
CARTOX	CAR-T-cell-therapy-associated TOXicity
CAV	cyclophosphamide, adriamycin, and vincristine
CFI	Chemotherapy-free interval
CFR	US Code of Federal Regulations
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CYP3A	cytochrome P450 3A
DCR	disease control rate
DILI	drug-induced liver injury
DLL3	delta-like ligand 3
DMC	data monitoring committee
DOR	duration of response
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

eGFR	estimated glomerular filtration rate
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOI	end of infusion
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30
EORTC-QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
EOT	end of treatment
EP	platinum-etoposide
EQ5D-5L	5-level EuroQol 5-dimension
ES	extensive stage
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy – General
FDA	US Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	formalin-fixed, paraffin-embedded
FIH	first-in-human
FNA	fine needle aspiration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBV	hepatitis B-virus
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLE	half-life extended
HR	hazard ratio
IBG	independent biostatistics group
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
IEAS	interim efficacy analysis set
IEC	independent ethics committee
Ig	Immunoglobulin

IHC	Immunohistochemistry
INN	International Nonproprietary Name
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IV	Intravenous
LDH	lactate dehydrogenase
LS	limited stage
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MAR	missing at random
MMRM	mixed model for repeated measurement
mOS	median overall survival
MRI	magnetic resonance imaging
MUGA	multigated acquisition
N/A	Not applicable
NA	nuclear antigen
NCT	National Clinical Trial
NE	not evaluable
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OR	objective response
ORR	objective response rate
OS	overall survival
OSF	**other safety findings**
PCR	polymerase chain reaction
PD	progressive disease
PD-1	**programmed cell death 1**
PD-(L)1	programmed cell death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
P-gp	P-glycoprotein
PK	Pharmacokinetic
PR	partial response
PRO	patient-reported outcome

PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
QTc	corrected QT interval
QTL	quality tolerance limit
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
scFc	single chain fragment crystallizable
SCLC	small cell lung cancer
SCR	Screening
SD	stable disease
SFU	safety follow-up
SOC	standard of care
SS	**special situations**
TBL	total bilirubin
TLS	Tumor lysis syndrome
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
UTI	urinary tract infection
VAS	visual analogue scale

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. Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered on the CRF.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.1 and **Section** 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 LABORATORY			
Chemistry • Sodium • Potassium • Chloride • Bicarbonate or CO_2 • Total protein • Albumin • Calcium • Magnesium • Phosphorus • Glucose • BUN or serum urea • Creatinine • eGFR • TBL • Direct bilirubin • ALP • AST (SGOT) • ALT (SGPT) • Creatine kinase • Uric Acid (during screening and the first 2 cycles) • LDH (during screening and cycles **1 and cycle** 2 **only**)	**CBC with differential** • RBC • Hemoglobin • MCV • Platelets • WBC **Differentials** 5-part differential: • Lymphocytes • Monocytes • Eosinophils* • Basophils* • Total neutrophils* or (Segmented neutrophils and bands/stabs) 3-part differential if unable to perform 5-part: • Lymphocytes* • Granulocytes* • Monocytes* OR • Lymphocytes • Neutrophils • Mid-cell fraction	**Coagulation** • PT/INR • PTT or APTT **Urinalysis** • Blood • Protein • Glucose • Bilirubin **Endocrine safety** • TSH • FT4	**Other safety labs:** • HIV antibody testing • Pregnancy test (serum or urine)[a] • Amylase • Lipase • Hepatitis B DNA/ Hepatitis C RNA by PCR as needed • Hep B surface antigen • Hep B core antibody • Hep C virus antibody
CENTRAL LABORATORY			
[redacted]	**Other** • Tarlatamab PK • Anti-tarlatamab antibody • [redacted]		

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; APTT = activated partial thromboplastin time; BIL = bilirubin; BUN = blood urea nitrogen; CBC = complete blood count; CO_2 = carbon dioxide; [redacted]; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; EOT = end of treatment; FT4 = free T4; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCV = mean corpuscular volume; MDRD = Modification of Diet in Renal Disease; PCR = polymerase chain reaction; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; RDW = red cell distribution width; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT =serum glutamic-pyruvic transaminase; TBL = total bilirubin; TSH = thyroid-stimulating hormone; WBC = white blood cell count

* Local lab may report Granulocytes instead of Neutrophils, Eosinophils, and Basophils individually

[a] **Highly sensitive serum pregnancy test (for subjects of childbearing potential) at screening; serum or urine pregnancy test on day 1 of every cycle while receiving investigational product and then monthly following EOT until 60 days from the last tarlatamab dose. Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or as required per local laws and regulations.**

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, gamma-glutamyl transferase, haptoglobin
Hematology	Hemoglobin, Platelets, RBC Morphology, RBC Count, WBC Count, WBC Differential
Coagulation	PT, INR, APTT
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 D RNA, Hepatitis E RNA, 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, IgG, 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; Ag = antigen; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; DILI = drug-induced liver injury; EDA = early antigen; Ig = immunoglobulin; IgG = Immunoglobulin G; INR = international normalized ratio; LDH = lactate dehydrogenase; NA = nuclear antigen; PT = prothrombin time; RBC = red blood cell; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; VCA = viral capsid antigen; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

Data Monitoring Committee (DMC)

An independent external review committee, the Data Monitoring Committee (DMC) will review unblinded interim safety and efficacy data, and provide recommendations related to continuing, modifying, or stopping the study.

The DMC will review all available safety and efficacy data periodically every 6 months. An Independent Biostatistics Group (IBG) will provide the analyses to the DMC. The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC will not have any direct contact with study site personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master file at the conclusion of the study. Further details are provided in the DMC charter.

Data Access Plan (DAP) Team

The Data Access Plan (DAP) team will convene for decision-making when DMC's recommendation is to stop study early, either for futility or for success. Details will be included in a separate DAP charter document.

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 protocol amendments and changes to the informed consent document that Amgen distributes to the site. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

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 US Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. 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.

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 is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for 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.

Informed Consent Process

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

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

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the 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 ICF is to be signed and personally dated by the subject or a legally authorized representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

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 authorized 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 21 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 case report form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

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

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

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 sponsor's systems. The sponsor 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 sponsor 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 sponsor 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, or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work 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.

This study will be published within 1 year of completion of the study on https://www.clinicaltrialsregister.eu/.

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

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

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

The sponsor or designee will perform ongoing source data verification to confirm that data entered on 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 Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, investigational product[s], and/or

noninvestigational product[s]/auxiliary medicinal product[s] storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Quality tolerance limit (QTL) parameters will be predefined in the QTL definitions table to identify possible systematic issues that can impact participant safety and/or reliability of the study results. These predefined parameters will be monitored during the study. Important deviations from the QTL threshold limits for these parameters and remedial actions taken will be summarized in the clinical study report.

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 they have 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 via IRT (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, such as gender, race, and ethnicity).

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

transfer records, depending on the study. Also, current medical records must be available.

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

Elements to include:

- Subject files containing completed CRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the 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)/auxiliary medicinal 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.

Remote Source Data Review and Verification

If permitted by national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those patients who participate in the trial and who did not object to remote access to their medical records. A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorized access, access rights should be revoked once rSDR/V tasks have been completed for the trial. The EMR system should have an audit trail and be able to log information on who accessed data and when. Remote access to the EMR should only be possible using a two-factor authentication.

Study and Site Closure

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

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) by 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 statistical analysis plan (SAP).
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected **intentional** overdose of either study treatment or a concomitant medication. **Intentional o**verdose will be reported as an adverse event/serious adverse event **when** it is taken with possible suicidal/self-harming intent. Such **intentional** overdoses are to be reported regardless of sequelae **on the Events CRF**. **Accidental/unintentional overdose will be captured as a medication error.** • "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 preexisting 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 preexisting condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of

the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will then record all relevant adverse event/serious adverse event information in the Events case report form (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
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product(s), noninvestigational products/auxiliary medicinal product(s)
  - Assessment of relatedness to study-required activity and/or procedures is only required for Serious Adverse Events
  - Action taken; and
  - Outcome of event.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Events CRF.
- 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 5.0, which is available at the following location:

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

with the following exceptions: Cytokine release syndrome and ICANS will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) (Lee et al, 2019).

Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product(s), noninvestigational products/auxiliary medicinal product(s)and each occurrence of each adverse event. • The investigator is obligated to assess the relationship between investigational products, noninvestigational products/auxiliary medicinal product(s, study-required activity, and/or procedure(s), and each occurrence of each serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure 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 investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) because of a serious adverse event, this information must be submitted to Amgen.

- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed Events CRF.
- The investigator will submit any updated serious adverse event data to Amgen immediately and no later than 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the EDC system. • If the EDC system is unavailable, then the site will report the information to Amgen using a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event Contingency Report Form) (see Figure 11-1) immediately and no later than 24 hours of the investigator's awareness of the event. • **The primary mechanism for the site to report the Other Safety Finding/Special Situation associated with a serious adverse event to Amgen is by submitting the Clinical Trial electronic serious adverse events Contingency Report Form immediately and no later than 24 hours of the investigator's awareness of the event**. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC 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 no later than 24 hours of the investigator's awareness of the event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Report Form (paper-based form)

Completion Instructions
Clinical Trial Electronic Serious Adverse Event Contingency Report Form (paper-based form)
(For use for clinical trial studies using Electronic Data Capture [EDC])

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

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

Types of Events to be reported on this form

- **Serious Adverse Events (SAE), regardless of causal relationship to Investigational Product (IP)**
- **Other Safety Findings/Special Situations associated with a Serious Adverse Event (SAE)**

1. **Site Information**
   Site Number* – Enter your assigned site number for this study
   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested
2. **Subject Information**
   Subject ID Number* – Enter the entire number assigned to the subject
   Age at event onset, Sex, and Race – Enter the subject's demographic information
   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

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

3. **Serious Adverse Event OR Other Safety Finding/Special Situation associated with a Serious Adverse Event**
   Provide the date the Investigator became aware of this Information
   Other Safety Finding/Special Situation associated with a Serious Adverse Event*
   - If the Other Safety Finding (OSF)/Special Situation (SS) (medication error, misuse, abuse) is associated with a serious adverse event, **record/report the serious adverse event on the Events Case Report Form in the EDC system and report the associated OSF/SS using this paper-based Serious Adverse Event Contingency Report Form.**
   - **If the OSF/SS (medication error, misuse, abuse) is associated with a serious adverse event, in addition to completing section 3 of this form, please complete all other sections of this form (sections 1 – 10).**
   - **If the EDC system is not available to record/report the serious adverse event on the Events Case Report Form, then report both the OSF/SS and the associated serious adverse event using this form.**
   - Do not enter Pregnancy or Lactation exposures or Product Complaints on this form. These must be collected/reported per the study protocol.

   Serious Adverse Event Diagnosis or Syndrome*or Other Safety Finding/Special Situation with a Serious Adverse Event* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.
   - The entry of death is not acceptable, as this is an outcome.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria) rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**
   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.
   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.
   Is event serious?* – Indicate Yes or No. This is a mandatory field.
   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

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

FORM-494035, Effective Date: 30 Nov 2023, Version:8.0

Completion Instructions – Clinical Trial Electronic Serious Adverse Event Contingency Report Form (for use for clinical trial studies using Electronic Data Capture [EDC])

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

Relationship to investigational device (Amgen investigational device and/or a non-Amgen investigational device)* – The Investigator must determine and enter the relationship of the event to the device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen or non-Amgen investigational device, this is a mandatory field.**

Please note, this question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps).

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

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

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

4. **Hospitalization**

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

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

5. **IP Administration including Lot # and Serial # when known / available.**

Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label

Initial Start Date – Enter date the product was first administered, regardless of dose.

Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

Action Taken with Product – Enter the status of the product administration.

6. **Concomitant Medications**

Indicate if there are any medications.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is co-suspect in the event

Continuing – Indicate if the subject is still taking the medication

Event Treatment – Indicate if the medication was used to treat the event

7. **Relevant Medical History**

Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. **Relevant Laboratory Tests**

Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

9. **Other Relevant Tests**

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

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

10. **Case Description**

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

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

FORM-494035, Effective Date: 30 Nov 2023, Version:2.0

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

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

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

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

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

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

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

3. SERIOUS ADVERSE EVENT or Other Safety Finding/Special Situation associated with a Serious Adverse Event

Provide the date the Investigator became aware of this information: Day_____ Month_____ Year_____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report OR Other Safety Finding/Special Situation associated with a Serious Adverse Event *List one event per line.*	Date Started (Day Month Year)	Date Ended (Day Month Year)	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP or the investigational medical device? Tarlatamab No✓	Tarlatamab Yes✓	Lurbinectedin No✓	Lurbinectedin Yes✓	Topotecan No✓	Topotecan Yes✓	Amrubicin No✓	Amrubicin Yes✓	Outcome of Event •Resolved •Not resolved •Fatal •Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

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

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

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

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For Restricted Use

Site Number	Subject ID Number

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

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

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

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

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

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

Test											
Date (Day Month Year)	Unit										

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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

Site Number	Subject ID Number

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

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

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

Study-specific contraception requirements for male 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 **60** days after the last dose of tarlatamab (Note: contraception requirements for standard of care [SOC] therapies are based on regional prescribing information).

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal 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 1 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, or implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with investigational product[s] and/or non-investigational product[s]/auxiliary medicinal product[s]; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional **60** days after the last dose of tarlatamab (Note: contraception requirements for SOC therapies are based on regional prescribing information)

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

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) through **60** days after the last dose of tarlatamab (Note: pregnancy requirements for SOC therapies are based on regional prescribing information).

- 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 investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s) through **60** days after the last dose of tarlatamab. 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 poststudy 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 or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional **60** days after the last dose of tarlatamab, 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 with pregnant partners or whose partners become pregnant during treatment and for an additional **60** days after the last dose of tarlatamab must practice sexual abstinence or use a condom through **60** days after the last dose of tarlatamab.
- 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 investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) through **60** days after the last dose of tarlatamab (Note: breastfeeding requirements for SOC therapies are based on regional prescribing information).
- 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 the exclusion criteria (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 investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) through **60** days after the last dose of tarlatamab.

Figure 11-2. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20210004

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: 20210004

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

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

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 small cell lung cancer (SCLC), the dose response and/or prediction of response to study treatment, 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, [redacted] and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the

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

11.7 Appendix 7. Reporting and Management of Potential Hepatotoxicity

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

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

11.7.1 Criteria for stopping Amgen Investigational Product and Noninvestigational product(s)/Auxiliary Medicinal Product(s) Due to Potential Hepatotoxicity

Stopping rules apply to **each of the following criteria in** subjects for whom another cause **for the** changes in liver biomarkers (TBL, INR and transaminases) has not been identified:

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

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

11.7.2 Reporting Criteria

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

- The event is to be reported to Amgen as a serious adverse event immediately and no later than 24 hours **after** discovery or notification of the event (ie, before additional etiologic investigations have been concluded)**.**
- The appropriate case report form (CRF) (eg, Events **electronic case report form [**eCRF**]**) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen**.**

Other events of **potential** hepatotoxicity 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).

11.7.3 Follow-up Actions

All subjects in whom investigational product(s) or noninvestigational product(s)/auxiliary medicinal product(s) is/are **interrupted** (either permanently or conditionally) due to potential **hepatotoxicity should** undergo a period of "close observation" until **elevated laboratory values** return to normal **ranges** 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 **in which laboratory values are still elevated perform repeat measurement of liver laboratory tests every 2 to 3 days until laboratory abnormalities improve**

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

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

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

Initiate investigation of alternative causes for **hepatotoxicity (Section 11.7.3.1.1)**

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

11.7.3.1 Investigating Alternative Causes of Hepatotoxicity

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

- blood count with differential to assess for eosinophilia**.**
- serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis.
- serum acetaminophen (paracetamol) levels.
- a more detailed history of:
  - prior and/or concurrent diseases or illness

- exposure to environmental and/or industrial chemical agents
- symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever.
- prior and/or concurrent use of alcohol, recreational drugs, and special diets.
- concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms

- viral serologies.
- creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear.
- appropriate liver imaging if clinically indicated.
- appropriate blood sampling for PK analysis if this has not already been collected.
- hepatology consult (appropriate liver biopsy may be considered in consultation with a hepatologist).

11.7.3.1.1 Important Alternative Causes

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

- hepatobiliary tract disease
- viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, **c**ytomegalovirus, **h**erpes **s**implex **v**irus, **v**aricella, **t**oxoplasmosis, and **p**arvovirus)
- 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 **s**yndrome, 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
- **NASH (**nonalcoholic fatty liver disease **AKA metabolic dysfunction-associated steatohepatitis [MASH])** including steatohepatitis)
- non**-**hepatic causes (eg, rhabdomyolysis, hemolysis)

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

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

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

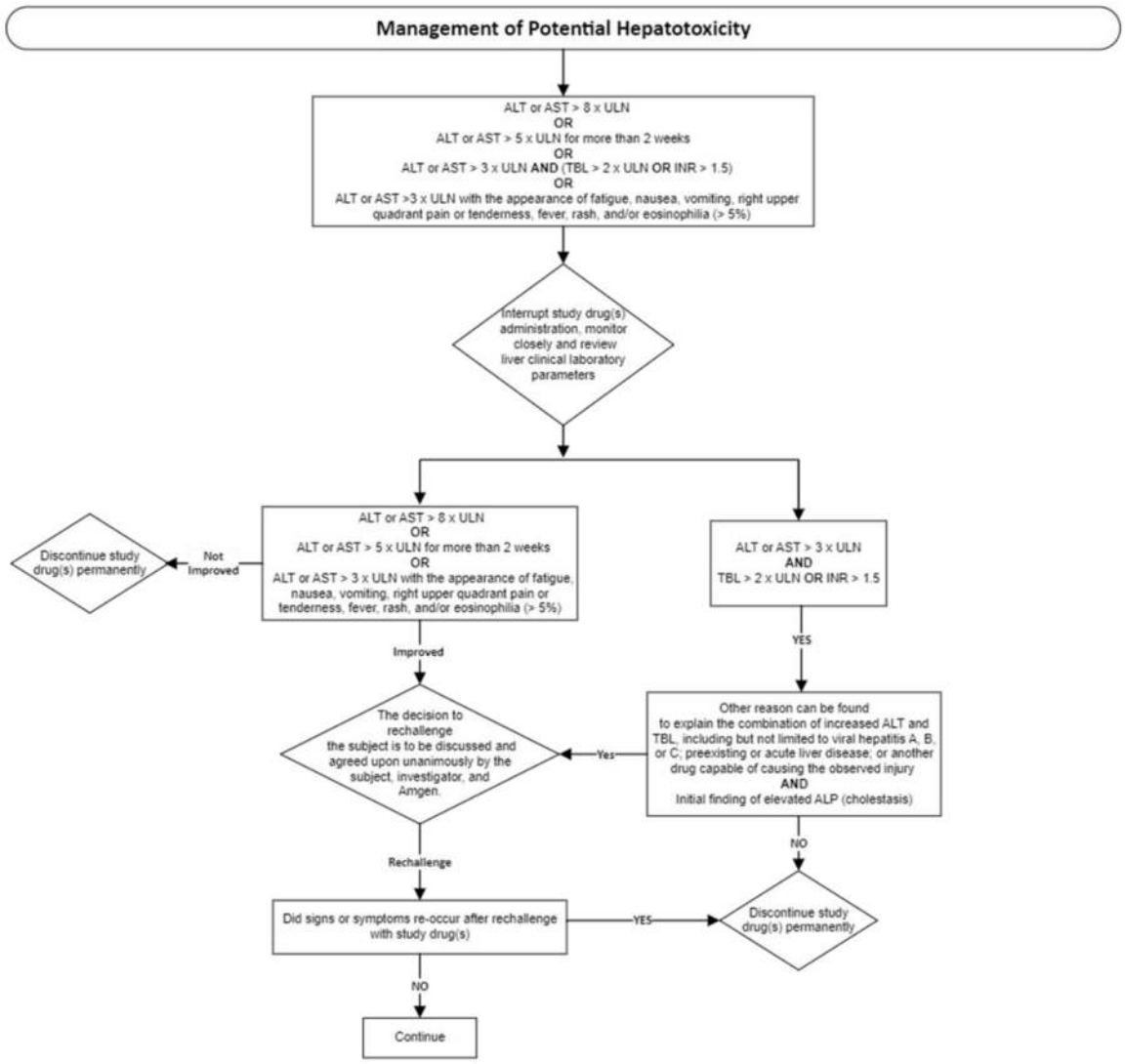
- The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen. **If rechallenge is considered appropriate, the subject must be fully informed about the risk and should give written consent. Any rechallenge must be accompanied by close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

11.7.5 Permanent Discontinuation of Study Drug(s)

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

11.7.6 Management Flow Chart

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



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

11.8 Appendix 8. Protocol-specific Anticipated Serious Adverse Events

Anticipated serious adverse events are events that are anticipated to occur in the study population at some frequency independent of investigational product exposure and do not need to be reported individually as a US FDA Investigational New Drug (IND) safety report by the sponsor. Identification and reporting of anticipated serious adverse events is the responsibility of the sponsor; the investigator is responsible for reporting adverse events and serious adverse events as described in Section 8.4.6 and Section 11.4.

Anticipated Serious Adverse Events for Study 20210004

MedDRA Preferred Term[a]
Cytokine release syndrome
Immune effector cell-associated neurotoxicity syndrome
Neutropenia

[a] Exact Preferred Term according to MedDRA Version 27.0

11.9 Appendix 9. Eastern Cooperative Oncology Group (ECOG) Performance Status and New York Heart Association (NYHA) Functional Classification

Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

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

New York Heart Association (NYHA) Functional Classification

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

11.10 Appendix 10. Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1); Eisenhauer et al, 2009

11.10.1 Definitions

11.10.1.1 Measurable Disease

The presence of at least 1 measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

11.10.1.2 Measurable Lesions

11.10.1.2.1 Measurable Non-nodal Tumor Lesions

Non-nodal lesions with clear borders that can be accurately measured in at least 1 dimension with longest diameter ≥ 10 mm in computed tomography (CT)/magnetic resonance imaging (MRI) scan with slice thickness no greater than 5 mm. When slice thickness is greater than 5 mm, the minimum size of measurable lesion should be twice the slice thickness.

11.10.1.2.2 Nodal Lesions

Lymph nodes are to be considered measurable if ≥ 15 mm in short axis when assessed by CT/MRI (scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

11.10.1.2.3 Cystic Lesions

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above for non-nodal lesions.

11.10.1.2.4 Bone lesions with identifiable soft tissue components

Bone lesions with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above for non-nodal lesions.

11.10.1.2.5 Clinically Measured Lesions

Visible or palpable lesions can be considered measurable if ≥ 10 mm in longest diameter for non-nodal or ≥ 15 mm in shortest diameter for lymph nodes. Lesions should be measured radiologically if more accurate, if not then measured by calipers.

11.10.1.2.6 Irradiated Lesions

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not measurable unless there has been demonstrated progression that is measurable in the lesion prior to enrollment.

11.10.1.3 Non-measurable Lesions

All other lesions, including small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with $\geq$ 10 mm to $<$ 15 mm short axis with CT scan slice thickness no greater than 5 mm) are considered non-measurable. (When slice thickness is greater than 5 mm, the minimum size of measurable lesion should be twice the slice thickness).

Other examples of lesions usually considered to be non-measurable 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.
- Categorically, clusters of small lesions, bone lesions without a soft tissue component, inflammatory breast disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis and leptomeningeal disease are non-measurable.

11.10.2 Methods of Measurement

All measurements should be taken and recorded in metric notation, using a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and throughout the trial. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will be assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.10.2.1 CT/MRI

Contrast-enhanced CT or MRI should be used to assess all lesions. Optimal visualization and measurement of metastasis in solid tumors requires consistent administration (dose and rate) of intravenous (IV) contrast as well as timing of scanning. CT and MRI should be performed with $\leq$ 5 mm thick contiguous slices. The longest diameter of selected lesions should be measured in the plane in which the images were acquired. Ideally, the same scanner or at least type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

11.10.2.2 PET-CT

At present, the low dose or attenuation correction CT portion of a combined positron emission tomography - computed tomography (PET-CT) is not always of optimal diagnostic CT quality for use with Response Evaluation Criteria in Solid Tumors (RECIST) measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

11.10.2.3 Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

11.10.2.4 Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR), or surgical resection is an endpoint.

11.10.2.5 Tumor markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize in a subject with a radiological CR for a subject to be considered a CR.

11.10.2.6 Cytology, Histology

These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the

neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease.

11.10.2.7 FDG-PET

While fluorodeoxyglucose - positron emission tomography (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progressive disease (PD) based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

11.10.3 Lesion Evaluation

11.10.3.1 Baseline documentation of “Target” and “Non-target” lesions

11.10.3.1.1 Target Lesions

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and suitability for accurate repeated measurements. All other measurable lesions will be followed as non-target lesions.
- Lymph nodes are considered 1 organ, thus a maximum of 2 measurable lymph nodes may be identified as target lesions.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference by which to characterize objective tumor response.

11.10.3.1.2 Non-Target Lesions

- All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should be recorded at baseline. These lesions should be followed as “present,” “absent,” “unequivocal progression,” or “not evaluable” throughout the study. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (eg, “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

11.10.4 Response Criteria

Table 11-3. Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target non-nodal lesions. Any target lymph node must have reduction in short axis to < 10 mm, NOT total disappearance.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. If a subject is missing lesion data at a disease assessment and yet progressive disease criteria is met despite the missing data, the subject will be classified as PD.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not Evaluable (NE)	When inadequate or no imaging/measurement is done at a particular time point, the subject's response is not evaluable (NE) at that time point.

Table 11-4. Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-nodal non-target lesions and normalization of tumor marker level. All non-target lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of 1 or more non-target lesions(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions[a]. If a subject is missing lesion data at a disease assessment and yet unequivocal progression is met despite the missing data, the subject will be classified as PD.
Not Evaluable (NE)	When inadequate or no imaging is done at a particular time point, the subject's response is not evaluable (NE) at that time point.

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

11.10.5 Evaluation of Best Overall Response

The subject's best response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions and confirmation of response. Best overall response (BOR) will be based on all post-baseline disease assessments that occur prior to the initiation of subsequent anticancer treatment. At least 5 weeks from the **date** of **randomization** must elapse without radiological disease progression to meet the minimum criteria for SD duration in order to assign a BOR of SD. In general, subjects not classifiable under the RECIST 1.1

response categories due to inadequate data or early death will be classified as non-evaluable (NE) for BOR but will be counted in the denominator of all response rate calculations.

Table 11-5. Time Point Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Subjects with Target (± Non-target) Disease			
CR	CR or NA	No	CR
CR	Non-CR/non-PD or NE	No	PR
PR	CR or Non-CR/Non-PD or NE or NA	No	PR
SD	CR or Non-CR/Non-PD or NE or NA	No	SD
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NE	CR or Non-CR/Non-PD or NE or NA	No	NE
Subjects with Non-target Disease Only			
NA	CR	No	CR
NA	Non-CR/Non-PD	No	SD (Non-CR/Non-PD)[a]
NA	CR or Non-CR/Non-PD	NE	SD (Non-CR/Non-PD)[a]
NA	PD	Any	PD
NA	Any	Yes	PD
NA	NE	No	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease.

[a] Per RECIST v1.1, “SD (Non-CR/Non-PD)” is preferred over “SD” for Non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 11-6. Best Overall Response (BOR) When Confirmation of Complete Response (CR) and Partial Response (PR) Required

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

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

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

11.10.6 Special Notes on Response Assessment

- Target lesions that become "too small to measure" – While on study, all lesions (nodal and non-nodal) recorded at baseline should have their measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the non-lymph node lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions

based upon measurement error. To reiterate, however, if the radiologist is able to provide an accurate measure, that should be recorded, even if it is below 5 mm.

- New lesions – The term “new lesion” always refers to the presence of a new finding that is definitely tumor. If a new lesion is identified via a modality other than CT or MRI, CT or MRI confirmation is recommended unless the new lesion is deemed unequivocally tumor. New findings that are not definitively tumor but may be benign (infection, inflammation, etc,) are not selected as new lesions, until that time when the review is certain they represent tumor.
  - If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If additional imaging confirms there is definitely a new lesion, then progression should be declared using the date of the initial scan.
  - A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression, regardless of any response that may be seen in target or non-target lesions present from baseline.
- Any locoregional therapy not allowed per protocol
  - Any subject receiving locoregional therapy not allowed in the protocol while on study that directly affects 1 or more of the target lesions selected at baseline will be considered to be non-evaluable at all disease assessments that occur on or after the date of locoregional therapy with the exception of disease progression. However, if a lesion was completely resected where pathology was benign the subject will still be evaluable for response with 0 dimension reported.
  - If locoregional therapy was performed on a non-target lesion, that lesion will always be assessed as present unless pathology was benign.
- Lesions that split or coalesce on treatment - When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum and identified as a fragment of the original lesion. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".
- “Symptomatic deterioration” alone does not qualify as objective progression. If objective progression was not previously documented, then every effort should be made to document objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from scar or normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be further investigated by fine needle aspirate/biopsy, to confirm the CR status.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient’s response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient’s tumor had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and 1 lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently ‘disappeared’ single

lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria.

11.10.7 Confirmation Measurement

Confirmation of CR and PR is required and must occur no fewer than 4 weeks after initial documentation of CR or PR. If CR is pending confirmation and is designated at an assessment followed by 1 or more NE assessments, and/or PR assessments such that the Target Lesion Response is CR and the Non-Target Lesion Response is NE, CR may be confirmed thereafter if Non-Target Lesion Response returns to CR. Similarly, if a PR is pending confirmation and is designated at an assessment followed by 1 or more NE and/or SD assessments, PR may be confirmed thereafter. Subsequent Target Lesion Responses following a CR are limited to CR, PD, or NE; PD for target lymph nodes is met only if any lymph node target lesion reaches a short axis measurement of $\geq$ 15 mm.

11.11 Appendix 11. Specific Guidance for Cytokine Release Syndrome, Immune-effector Cell-associated Neurologic Syndrome, and Tumor Lysis Syndrome

11.11.1 Specific Guidance for Cytokine Release Syndrome

Cytokine release syndrome (CRS) is defined as a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction.

Clinical signs and symptoms of CRS are non-specific and may include a combination of the following:

- constitutional: fever ± rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
- skin: rash
- gastrointestinal: nausea, vomiting, diarrhea
- respiratory: tachypnea, hypoxemia
- cardiovascular: tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
- coagulation: elevated D-dimer, hypofibrinogenemia ± bleeding
- renal: azotemia
- hepatic: transaminitis, hyperbilirubinemia

The symptoms associated with the CRS event do not meet the definition of an adverse event as defined in Section 11.4. Therefore, the CRS associated event (ie, CRS, cytokine storm) should be documented on the Events electronic case report form (eCRF) as the diagnosis. However, since it is important to document all symptoms related to a CRS event, a CRS Symptoms eCRF will also be available to record the symptoms associated with each CRS event.

If the severity of a CRS event changes from the date of onset to the date of resolution, record a single event for each increased level of severity on the Events eCRF and fill out an associated CRS Symptoms eCRF. If the symptoms worsen enough to impact the overall CRS grade, it is important to remember to record a new CRS event on the Events eCRF with the appropriate grade.

Temperature may normalize within a few hours of treatment, whereas the other components of CRS take longer to resolve. Once such therapies are used, the patient is considered to still have CRS, even in the absence of fever, until all signs and symptoms

leading to the diagnosis of CRS have resolved. Likewise, CRS can be downgraded in an afebrile patient treated with anticytokine therapy as their hemodynamic status and/or hypoxia improves. Typically, a patient with severe CRS in whom fever, oxygen, and pressor requirements have resolved may be assumed to have resolved CRS unless there are alternative causes for the fever, hypoxia, and/or hypotension.

Refer to Table 6-2 for details regarding CRS grading and management. Refer to the regional prescribing information or institutional guidelines (if not addressed in prescribing information) for additional information regarding CRS/immune effector cell-associated neurotoxicity syndrome (ICANS) rescue therapy.

11.11.2 Specific Guidance for 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 chimeric antigen receptor T cells (CAR-T) therapies, symptoms of ICANS may be shared among immune effector cell-associated therapies such as bispecific T cell engager (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 11-7. 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

Assessment and Supportive Care Recommendations (all grades)

While management and treatment of ICANS has been developed mainly for patients treated with CAR-T therapies, the principles and therapies for ICANS management may be adapted to patients treated with BiTE molecules. Please refer to Table 6-2 for guidance on management based on the Immune Effector Cell Therapy Toxicity Assessment and Management (also known as CARTOX) for support in clinical decision making (https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf).

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

11.11.3 Tumor Lysis Syndrome

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 classifies tumor lysis syndrome (TLS) in grade 3 (present), grade 4 (life threatening consequences; urgent intervention indicated) and grade 5 (death). Cairo and Bishop developed a system for defining and grading TLS based on Hande-Garrow classification of laboratory or clinical TLS (Coiffier et al, 2008). In this trial, the Cairo-Bishop classification will be used to define presence of TLS, ie, presence of laboratory TLS (see Table 11-9) and clinical TLS. Final event grade will be assigned according to CTCAE version 5.0.

Based on the Cairo and Bishop system, laboratory TLS is defined as any 2 or more abnormal serum values present within 3 days before or 7 days after initiation of treatment in the setting of adequate hydration (with or without alkalinization) and use of a hypouricemic agent (Table 11-9).

Table 11-8. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

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

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

Clinical TLS requires the presence of laboratory TLS in addition to 1 or more of the following significant complications: renal insufficiency, cardiac arrhythmias/sudden death, and seizures.

Approval Signatures

Document Name: Protocol Amendment tarlatamab 20210004 4

Document Description: Tarlatamab 20210004 Protocol Amendment 4

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Reason for Signing: Management	Name: [redacted] Date of Signature: 19-Jul-2024 13:04:36 GMT+0000

Summary of Protocol Changes

Protocol Amendment 4 19 July 2024

This protocol was mainly amended due to the evolving data and the availability of pooled population-pharmacokinetics (PK) analysis for tarlatamab to inform and update half-life. The contraception and lactation washout period for tarlatamab was adjusted to align with the Food and Drug Administration (FDA)'s recommended language in the U.S Prescribing Information (USPI). The new duration was set to 5 half-lives, equivalent to 2 months (60 days), after the last dose of tarlatamab for both male and female participants.

Changes including, but not limited to the following were incorporated into the protocol:

- Updated language for subjects with no exposure to prior anti-programmed cell death ligand 1 (PD-[L]1) to include the classification for non-use.
- Added language to specify that ad hoc vital status (survival status) collection may be required to support key study analysis.
- Updated the safety follow-up (SFU) period from 42 (+5) days to 60 (+5) days.
- Clarified the time points for collecting PK and antibody samples.
- Clarified that New York Heart Association (NYHA) assessments collection for screening is only to be performed for subjects with a known history of congestive heart failure to verify exclusion 207.
- Specified that serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen during the long-term follow-up (LTFU) phase. Language was added to specify that after end of study serious adverse events suspected to be related to investigational product will be reported to Amgen.
- Clarified collection timepoints by adding a window of 7 days in every 6-week (Q6W) visit to allow collection of the [redacted] on the same visit.
- Updated the radiological imaging and tumor assessment period to 7 days (previously: 3 days).
- Updated the timeframe for using contraception following the last dose of tarlatamab throughout the protocol, which has now been extended to 60 days for female subjects (previously: 72 days) and 60 days for male subjects and their female partners (previously: 132 days).
- Updated monitoring guidance to include details for Cycle 2+.
- Updated the non-Amgen investigational product information to remove details of strengths and formulation.
- Revised the language for live and live-attenuated vaccines to depict that they are prohibited for a further 60 days after last dose (previously: 42 days).
- Revised the language regarding treatment; post progression to clarify this is permitted for the standard of care arm as well and removed the requirement for radiation therapy.
- Clarified the action required for step-dose rechallenge after tarlatamab delay.
- Revised the language for discontinuation of study treatment to clarify that at minimal vital status (survival status) should be collected, through as an example, direct or family

member contact or family members contact or through the attending physician or medical records, public registries, and public records, subject to local laws and regulations.

- Revised the language for subject discontinuation/withdrawal from the study to clarify that the subject is not considered to have ended the study until there is no means to continue collection of vital status (survival status).
- Clarified the actions to be taken if a subject failed to return to the clinic for a required study visit.
- Updated end of treatment and SFU language to clarify that a subject at minimum should be followed via telephone, clinic visit, or chart review to assess for survival and/or the commencement of subsequent cancer therapy.
- Added information about hypersensitivity reactions (signs, symptoms, and management) based on the latest available data.
- Aligned the adverse event grading scale to be used for Cytokine release syndrome and immune effector cell-associated neurologic syndrome (ICANS).
- Provided examples of local regulatory requirements for reporting suspected unexpected serious adverse reactions (SUSARs).
- Section updated to depict that the patient-reported outcome (PRO) analysis set based on the intent-to-treat (ITT) population and not the PRO analysis set, to avoid potential bias when making direct comparisons between treatment arms, per regulatory health authority recommendations.
- Updated hepatotoxicity language per guidance to capture the new stopping rules and flowchart to align with cited FDA guidance. Updated language.
- General editorial changes, including administrative, abbreviations, typographical, and formatting corrections were made throughout the protocol for clarification.

Changes From Protocol Amendment 3 to Superseding Protocol Amendment 3:

On 14 December 2023, Protocol Amendment 3 was superseded to add a collection of Tumor Tissue (at screening and end of treatment) to the Standard of Care Schedule of Activities.

- To highlight that the rationale for the update to the language in Section on Sample Size Determination, and Overall Survival was to remove one Interim analysis.

This protocol was amended to:

- Update the safety monitoring guidelines to ensure subject safety when receiving tarlatamab, in alignment with data presented to and in agreement with regulatory agencies.
- Update the collection of patient reported outcomes to include an indication of taste changes, in agreement with regulatory agencies.
- Update the study rationale, dose justification, and benefit/risk profile based on the latest
- data regarding antitumor activity in subjects with extensive stage small cell lung cancer (ES-SCLC) in a phase 2 and phase 1 study.
- Remove the “Sucrose mediated renal impairment” potential risk of Tarlatamab based on updated data (Global).
- Update the Schedule of Activities to ensure assessment timing and collection is performed as intended to achieve the goals of the study.
- Update the eligibility criteria for stricter guidance on hepatitis B and C exclusion criteria.
- Update the eligibility criteria on brain metastasis exclusion criteria.
- Update the eligibility criteria with clarification on “mixed histology” exclusion criteria.
- Update in the recommendation guidelines for the management of cytokine release syndrome (CRS) to include the consideration for administration of dexamethasone in grade 1 and 2 CRS.
- To update Dose modification guidelines for ICANS and related neurological events and seizures in alignment with Immune Effector Cell Toxicity Assessment and Management (also known as CARTOX) guidelines.
- To remove language that disease progression of SCLC and death due to disease progression are not considered and reported as adverse events or serious adverse events as this does not apply to studies that are ongoing.
- To update the language in Regulatory Reporting Requirements for Safety Information to incorporate language in alignment across Amgen protocols.
- Other administrative, typographical, abbreviation, and formatting changes were made throughout the protocol for consistency and clarification as needed.

Protocol amendment 3 11 December 2023

This protocol was amended to:

- Update the safety monitoring guidelines to ensure subject safety when receiving tarlatamab, in alignment with data presented to and in agreement with regulatory agencies.
- Update the collection of patient-reported outcomes to include an indication of taste changes, in agreement with regulatory agencies.
- Update the study rationale, dose justification, and benefit/risk profile based on the latest data regarding antitumor activity in subjects with extensive stage small cell lung cancer (ES-SCLC) in a phase 2 (Study 20200491) and phase 1 study (Study 20160323).
- Remove the “Sucrose mediated renal impairment” potential risk of Tarlatamab based on updated data (Global).
- Update the Schedule of Activities to ensure assessment timing and collection is performed as intended to achieve the goals of the study.
- Update the eligibility criteria for stricter guidance on hepatitis B and C exclusion criteria.
- Update the eligibility criteria on brain metastasis exclusion criteria.
- Update the eligibility criteria with clarification on “mixed histology” exclusion criteria.
- Update in the recommendation guidelines for the management of cytokine release syndrome (CRS) to include the consideration for administration of dexamethasone in grade 1 and 2 CRS.
- Update dose modification guidelines for ICANS and related neurological events and seizures in alignment with Immune Effector Cell Toxicity Assessment and Management (also known as CARTOX) guidelines.
- Remove language that disease progression of SCLC and death due to disease progression are not considered and reported as adverse events or serious adverse events as this does not apply to studies that are ongoing.
- Update the language in Regulatory Reporting Requirements for Safety Information to incorporate language in alignment across Amgen protocols.
- Make other administrative, typographical, abbreviation, and formatting changes throughout the protocol for consistency and clarification as needed.

Protocol Amendment 2 **06 September 2023**

The study was updated based on the latest data obtained from the Phase 2 Study to

• Include a reduction in monitoring to [redacted] hours after cycle 1 day 1 (C1D1) and cycle 1 day 8 (C1D8).
• Remove the requirement for evaluable tumor as an inclusion criterion, based on analysis of the relationship between delta-like ligand 3 (DLL3) expression and the efficacy seen.
• Reduce the sample size.

The protocol was amended to:

• Remove the requirement of pre-screening period and tissue biopsy with an allcomers strategy.
• Update the number of subjects to [redacted] subjects, approximate number of sites to 240, and total study duration to approximately 4 years.
• Remove the requirement for hospitalization post-infusion and replace with reduced monitoring guidance.
• Update the topotecan (China) intravenous dose to 1.2 mg/m2 or other locally approved dose.
• Update the schedule of activities table:
– to remove pre-screening (archival tumor tissue/biopsy), C-reactive protein, ferritin, and endocrine panel
– to add demographics information, prior therapies review, thyroid stimulating hormone, free T4 assessments, and tumor tissue collection assessments
– to update physical examination to inform that weight must be collected at each day 1, vital signs and pulse oximetry, and pharmacokinetic and anti-tarlatamab antibody collection windows
– to update urinalysis, 12-lead electrocardiogram (ECG), hematology, and chemistry panel assessments.
• Remove exploratory objectives and endpoints.
• Update the inclusion/exclusion criteria:
– to include subjects with histologically or cytologically confirmed small cell lung cancer (SCLC) with demonstrated progression or relapse
– to include subjects with prothrombin time (PT)/international normalized ratio (INR) and partial thromboplastin time (PTT) or activated partial thromboplastin time (APTT) ≤1.5 x institutional upper limit of normal (ULN) except for subjects undergoing oral anticoagulation using vitamin K antagonists
– to clarify that subjects must be on a stable dose of anticoagulant therapy for 2 weeks prior to enrollment
– to exclude subjects with prior therapy with tarlatamab or any of the standard of care (SOC) chemotherapy included as part of this trial or in any tarlatamab clinical trial.
• Update that product lot number will be recorded at the site level for SOC chemotherapy.

• Update the supply information for topotecan Accord and Hydrochloride (AoLuoNa) injection.
• Add a reference to the regional prescribing information or institutional guidelines for additional information regarding rescue medication.
• Rephrase “dose change” and replace with tarlatamab and SOC chemotherapy “delay or discontinuation”.
• Update the tarlatamab and dose modification guidelines for adverse events.
• Update the details regarding vital signs and pulse oximetry.
• Add that whole blood samples will be collected for immunophenotyping by flow cytometry in approximately 200 subjects (100 patients per arm) to identify changes in peripheral immune cell subsets and activation status.
• Clarify that further details of the censoring rules will be described in the statistical analysis plan (SAP).
• Remove details regarding progression-free survival (PFS) Censoring Rule.
• Add that the local laboratory may report granulocytes instead of neutrophils, eosinophils, and basophils individually.
• Remove the Cairo Bishop grading of tumor lysis syndrome.
• Align protocol-required therapy language with language from the latest clinical protocol template.
• Update the National Clinical number of the study.

Protocol Amendment 1 **30 May 2023**

Protocol amendment 1 was made mainly to address feedback received from the regulatory agency. Changes driven by regulatory feedback are listed below.

• Provided additional language to clarify the purpose for having an optional pre-screening phase in the study. This pre-screening phase allows for an early assessment of tumor biopsy, early identification of eligible subjects, and consequently a reduction in the time between the last cycle of first-line therapy and the first treatment within the study.

• Specified that serum pregnancy test at screening must be performed within 7 days of cycle 1 day 1 and all additional pregnancy tests (serum or urine) must be performed at day 1 of each cycle and reviewed before treatment administration.

• Updated eligibility criteria for patients who have progressed or recurred following 1 platinum-based regimen to add that only patients who per investigator discretion are candidates for the 3 standard of care therapies should be included.

• Added that after completion of tarlatamab treatment, live and live-attenuated vaccines are prohibited for 42 days after last dose of tarlatamab.

• Updated tarlatamab dose modification guidelines for adverse events to:

– Add specific guidelines for administration of corticosteroids by specifying dosing of corticosteroids (8 mg to 16 mg of dexamethasone or equivalent) and frequency of administration (every 8 hours) to manage neurologic events.
– Clarify that for neurological events grade 4, tarlatamab administration must be permanently discontinued rather than interrupted/delayed.

• Other administrative changes were included in this protocol amendment which represented general corrections or clarifications. These changes are listed below.

– Informed in the protocol that the clinical study will be published within 1 year of completion on clinicaltrialsregister.eu.
– Clarified that subjects in China randomized to standard of care therapy will receive topotecan at a lower intravenous dose.
– Updated Schedule of Activities tables for adverse events, serious adverse events, and concomitant therapy to correctly show timing on which of these assessments are to be completed.
– Updated Schedule of Activities tables for vital signs, pulse oximetry assessment to clarify collection time.
– [redacted]
– Updated hospitalization and monitoring guidance for cycle 2 from “8 hours” to “6 to 8 hours” to maintain consistency across cycle 1 and cycle 2 observation hours.
– Aligned collection and reporting of safety events with current procedures.
– Corrected administrative errors in the Schedule of Activities tables to ensure alignment between tables and footnote details.
– Corrected minor errors related to description of planned analyses.

- Incorporated administrative and editorial changes (including document version date, grammatical, typographical, abbreviations, and formatting) throughout the protocol.