## Title Page

| | | |
|---|---|---|
| **Protocol Title:** | | Phase 2a Study Evaluating the Efficacy, Safety, Tolerability and Pharmacokinetics of Tarlatamab in Chinese Subjects with Advanced Small Cell Lung Cancer after Two or More Prior Lines of Treatment (DeLLphi-307) |
| **Short Protocol Title:** | | Phase 2a Study Evaluating Tarlatamab in Chinese Subjects with Advanced Small Cell Lung Cancer after Two or More Prior Lines of Treatment (DeLLphi-307) |
| **Protocol Number:** | | 20230273 |
| **Investigational Product:** | | Tarlatamab (AMG 757) |
| **Trade Name:** | | Not Applicable |
| **Sponsor** | **Name of Sponsor:** | Amgen Inc. |
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| **EU CT Number:** | | Not Applicable |
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| **Data Elements Standards Version:** | 9.0 | |

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

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**Investigator's Agreement:**

I have read the attached protocol entitled Phase 2a Study Evaluating the Efficacy, Safety, Tolerability and Pharmacokinetics of Tarlatamab in Chinese Subjects with Advanced Small Cell Lung Cancer after Two or More Prior Lines of Treatment (DeLLphi-307), dated **06 September 2024**, and agree to abide by all provisions set forth therein.

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

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

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

Signature

Name of Investigator Date (DD Month YYYY)

Title and Role of Investigator

Institution Name

Address and Telephone Number of Institution

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# 1. Protocol Summary

## 1.1 Synopsis

**Protocol Title:** Phase 2a Study Evaluating the Efficacy, Safety, Tolerability and Pharmacokinetics of Tarlatamab in Chinese Subjects with Advanced Small Cell Lung Cancer after Two or More Prior Lines of Treatment (DeLLphi-307)

**Short Protocol Title:** Phase 2a Study Evaluating Tarlatamab in Chinese Subjects with Advanced Small Cell Lung Cancer after Two or More Prior Lines of Treatment (DeLLphi-307)

**Study Phase:** 2a

**Indication:** Small Cell Lung Cancer (SCLC)

**Study Rationale**

Small cell lung cancer (SCLC) is a grave diagnosis, marked by high initial response rates to platinum-based first-line chemotherapy. However, resistance to subsequent treatments quickly emerges, resulting in a median survival of 10 to 12 months post-diagnosis (Rudin et al, 2015). Delta-like ligand 3 (DLL3) is typically intracellular in normal tissues but often overexpressed on the cell surface in most SCLC tumors, making it an attractive target for T-cell therapies (Saunders et al, 2015). Notably, minimal cytoplasmic staining is observed in the brain, pituitary, and pancreatic islets in normal tissues (Study 123377), suggesting the potential for tumor-specific DLL3-targeted therapy.

Tarlatamab (INN; AMG 757) is a novel, extended half-life (HLE) bispecific T-cell engager (BiTE®) designed to direct T effector cells toward DLL3-expressing cells using a tandem single-chain fragment crystallizable (scFc) for prolonged half-life. In an ongoing phase 2 study (Study 20200491), tarlatamab has demonstrated efficacy in SCLC patients with a manageable safety profile (Ahn et al, 2023).

**Tarlatamab received accelerated approval from the United States Food and Drug Administration (FDA) for the treatment of adult patients with extensive-stage SCLC with disease progression on or after platinum-based chemotherapy.**

Study 20230273 aims to assess tarlatamab's efficacy, safety, tolerability, and pharmacokinetics (PK) in Chinese subjects with advanced SCLC who have progressed on or recurred following 1 platinum-based regimen as first-line (1L) therapy (including a Programmed Cell Death Protein 1 [PD-1]/Programmed Cell Death Ligand 1 [PD-(L)1]) and at least 1 other prior line of therapy (re-treatment with a platinum-based regimen is

considered a second-line of therapy). Detailed information about tarlatamab's chemistry, pharmacology, efficacy, and safety is available in the investigator's brochure.

**Objective(s) and Endpoint(s)/Estimand(s)**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • Evaluate efficacy of tarlatamab as assessed by objective response rate (ORR) based on blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) | • ORR BICR, defined as proportion with best overall response (BOR) of complete response (CR) plus partial response (PR) |
| **Secondary** | |
| • Evaluate efficacy of Tarlatamab as assessed by duration of response (DOR), disease control (DC), and progression-free survival (PFS) based on BICR per RECIST 1.1 | • DOR, defined as time from the first documentation of objective response (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<br>• DC, defined as CR + PR + stable disease (SD)<br>• Duration of DC, defined as time from the first documentation of CR, PR, or SD until the first documentation of disease progression or death due to any cause, whichever occurs first. Only subjects who have achieved CR, PR, or SD will be evaluated for Duration of DC<br>• PFS, defined as time from enrollment until disease progression or death from any cause, whichever occurs first. Progression will be based on RECIST 1.1. |
| • Evaluate efficacy of Tarlatamab as assessed by ORR, DOR, DC, and PFS based on investigator assessment per RECIST 1.1 | • ORR (Investigator)<br>• DOR<br>• DC<br>• Duration of DC<br>• PFS |
| • Evaluate efficacy of Tarlatamab as assessed by overall survival (OS) | • OS, defined as time from enrollment until death from any cause |

| | |
|---|---|
| • Evaluate safety and tolerability | • Incidence of treatment-emergent adverse events |
| • Characterize the pharmacokinetics of tarlatamab | • Serum concentration of tarlatamab |
| • Evaluate the immunogenicity of tarlatamab | • Incidence of anti-tarlatamab antibody formation |

**Estimand(s) for Primary Objective(s)**

Objective response rate (ORR) by blinded independent central review (BICR) per RECIST 1.1 in Chinese subjects with advanced SCLC who have progressed on or recurred following 1 platinum-based regimen as 1L therapy (including a PD-1/ PD [L]1) and at least 1 other prior line of therapy (re treatment with a platinum-based regimen is considered a second line of therapy) prior to start of new cancer therapy (while-on-treatment strategy).

**Overall Design**

This is a phase 2a, multicenter, single arm, open-label study in Chinese subjects with advanced SCLC who have progressed on or recurred following 1 platinum-based regimen as 1L therapy (including a PD-1/PD-[L]1) and at least 1 other prior line of therapy (re-treatment with a platinum-based regimen is considered a second-line of therapy).

The study consists of a 21-day screening period, a treatment period, a safety follow-up (SFU) period, and a long-term follow-up (LTFU) period. Enrolled subjects will receive tarlatamab per protocol.

**Number of Subjects**

Approximately 30 Chinese subjects are planned to be enrolled in the study.

**Summary of Subject Eligibility Criteria**

Male and female subjects who are residents in China and of Chinese ancestry, aged ≥ 18 years (or legal adult age), with confirmed advanced SCLC after 1 platinum-based regimen as 1L therapy (including PD-1/PD-[L]1) and at least one other prior line of therapy.

Upon study consent, subjects undergo protocol-mandated screening assessments to confirm eligibility. They must have measurable lesions (per RECIST 1.1) within 21 days before the first dose of study treatment and adequate organ function.

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

**Treatments**

Tarlatamab will be administered as a 60-minute (± 10 minutes) intravenous (IV) infusion with 1 mg step dose on cycle 1 day 1 (C1D1) followed by a 10 mg target dose on cycle 1 day 8 (C1D8), and cycle 1 day 15 (C1D15) in a 28-day cycle. Subsequent doses (10 mg) will be administered every 2 weeks (Q2W) (ie, cycle 2+ day 1/day 15 dosing) in a 28-day cycle.

- Monitoring during cycle 1:
  - 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 cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS) by a health care provider is required prior to discharge.
    - Subjects return to site on cycle 1 day 2 (C1D2) and cycle 1 day 9 (C1D9) 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.
  - Intravenous Hydration: 1 L normal saline over 2 to 4 hours following tarlatamab administration on C1D1 and C1D8.

**Statistical Considerations**

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

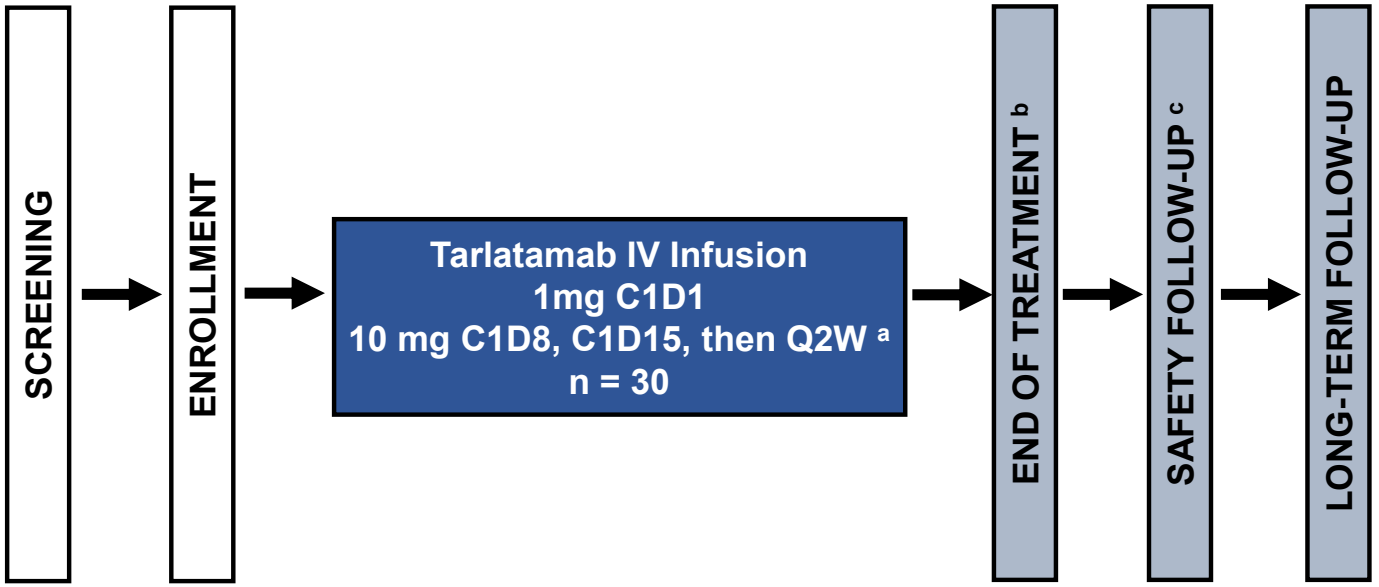
**Statistical Hypotheses**

No statistical hypotheses will be tested.

Sponsor Name: Amgen Inc.

## 1.2 Study Schema

**Figure 1-1. Study Schema**




C1D1 = cycle 1 day 1; C1D8 = cycle 1 day 8; C1D15 = cycle 1 day 15; IV = intravenous; Q2W = every 2 weeks; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1

[a] Subjects will receive study treatment until blinded independent central review (BICR)-**confirmed** disease progression per RECIST 1.1, death, withdrawal of consent, start of new anticancer therapy, unacceptable toxicity, or end of study as determined by the sponsor (whichever occurs first).

[b] End of Treatment visit will occur at the time the decision is made to discontinue study treatment (preferably within 14 days after last dose of study treatment) and prior to start of new anti-cancer therapy.

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

## 1.3 Schedule of Activities (SoA)

**Table 1-1. Schedule of Activities: Cycle 1 only**

| Procedure[a] | Screening | Treatment Period[b] | | | | | As clinically indicated | Notes |
|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | |
| Day | (Up to 21 Days Before Day 1) | 1 | 2 | 8 | 9 | 15 | | |
| **GENERAL AND SAFETY ASSESSMENTS** | | | | | | | | |
| Informed consent | X | | | | | | | |
| Inclusion and exclusion criteria | X | | | | | | | |
| Medical history | X | | | | | | | Includes medical, surgical, and cancer. |
| Demographics | X | | | | | | | |
| Physical examination (including neurological exam) | (X) | [X] | X | X | X | X | X | Physical exam must be completed prior to start of infusion on treatment days.<br>(X): Height to be collected at screening ONLY.<br>[X]: Must include weight on Day 1. |
| Vital Signs | X | (X) | X | (X) | X | X | X | Includes systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature.<br>(X): Refer to Section 8.4.1 for detailed vital sign collection time points. |
| ECOG PS | X | X | | | | | | |

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Footnotes defined on last page of this table.

## Table 1-1. Schedule of Activities: Cycle 1 only

| Procedure[a] | Screening | Treatment Period[b] | | | | | As clinically indicated | Notes |
|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | |
| Day | (Up to 21 Days Before Day 1) | 1 | 2 | 8 | 9 | 15 | | |
| NYHA | X | | | | | | | Collected at screening **only for patients with a known history of heart disease**. |
| ECG | X | | | | | | X | |
| ECHO or MUGA scan | X | | | | | | X | |
| Adverse events | | continuous | | | | | X | |
| Serious adverse events | continuous | | | | | | X | |
| Prior and Concomitant therapies review | continuous | | | | | | X | |
| **LABORATORY ASSESSMENTS** | | | | | | | | |
| HIV, Hepatitis B and C screening | 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 should be collected. |
| Coagulation[d] | X | X | | X | | X | X | |
| Hematology[d] | X | X | | X | | X | X | |
| Chemistry[d] | X | (X) | | X | | X | X | (X): Includes LDH and uric acid. |

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Footnotes defined on last page of this table.

**Table 1-1. Schedule of Activities: Cycle 1 only**

| Procedure[a] | Screening | Treatment Period[b] | | | | | As clinically indicated | Notes |
|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | |
| Day | (Up to 21 Days Before Day 1) | 1 | 2 | 8 | 9 | 15 | | |
| Urinalysis[d] | X | X | | | | | X | |
| Lipase and amylase[e] | X | X | | | | | X | |
| TSH and FT4[e] | X | X | | | | | X | |
| **CENTRAL LABORATORY ASSESSMENTS** | | | | | | | | |
| PK sample | | X | | | | | | X: Collect pre dose sample on C1D1.<br><br>The time of dosing and PK sample collection should be accurately recorded. |
| Anti-tarlatamab antibody sample | | X | | | | | | X: Collect pre dose sample on C1D1.<br><br>Refer to Section 8.7 for additional details. |
| **IMAGING ASSESSMENTS** | | | | | | | | |
| MRI brain | X[f] | | | | | | X | All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. Subsequently after screening, MRI brain can be performed at any time if clinically indicated per standard of care. |

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Footnotes defined on last page of this table.

**Table 1-1. Schedule of Activities: Cycle 1 only**

| **Procedure**[a] | **Screening** | **Treatment Period**[b] | | | | | **As clinically indicated** | **Notes** |
|---|---|---|---|---|---|---|---|---|
| | | **Cycle 1** | | | | | | |
| **Day** | **(Up to 21 Days Before Day 1)** | **1** | **2** | **8** | **9** | **15** | | |
| Radiological imaging and tumor assessment[g] | X[f] | Weeks 1 to 48: Q6W (± 1 week)<br>Weeks 49+ Q12W (± 1 week)<br>by BICR per RECIST 1.1 | | | | | X | Refer to Section **8.3.1** for additional details.<br>For subjects who end study treatment for reasons other than specified in Section 8.3.2, every effort should be made to perform scheduled radiographic imaging (CT/MRI) until radiographic progression. |
| **STUDY TREATMENT AND MONITORING** | | | | | | | | |
| Other protocol-required therapy: Dexamethasone | | X | | X | | | | Refer to Section 6.1.2 for details for pre-treatment with dexamethasone (or equivalent dose of other corticosteroids). Dexamethasone will be administered within 1 hour prior to tarlatamab infusion on days 1 and 8 of cycle 1 only. |
| Tarlatamab Infusion | | X | | X | | X | | |

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Footnotes defined on last page of this table.

**Table 1-1. Schedule of Activities: Cycle 1 only**

| Procedure[a] | Screening | Treatment Period[b] | | | | | As clinically indicated | Notes |
|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | |
| Day | (Up to 21 Days Before Day 1) | 1 | 2 | 8 | 9 | 15 | | |
| Monitoring post-tarlatamab infusion | | X | | 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, additional monitoring may be recommended post-tarlatamab infusion based on occurrence of CRS, ICANS, or ICANS-related neurological events. Refer to Table 6-1. |
| Other protocol-required therapy: IV hydration | | X | | X | | | | Refer to Section 6.1.2 for details related to IV hydration. IV hydration (1 L normal saline) over 2 to 4 hours following tarlatamab administration. |

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BICR = Blinded Independent Central Review; 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; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; FT4 = free T4; HIV = human immunodeficiency virus; ICANS = immune effector cell-associated neurotoxicity syndrome; IV = intravenous; LDH = Lactate dehydrogenase; MUGA Scan = multigated acquisition scan; MRI = magnetic resonance imaging; NYHA = New York Heart Association; PK = pharmacokinetic; Q6W = every 6 weeks; Q12W = every 12 weeks; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1; TSH = thyroid-stimulating hormone

[a] All procedures and assessments on dosing days are to be completed prior to study drug administration unless otherwise indicated. Assessments should not be performed from the infusion line.

[b] Each visit week and day is relative to day 1 of each cycle. Cycle 1 visits have a ± 1-day window from designated time point unless otherwise specified.

[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 cycle 1 day 1 **dose, pre-infusion cycle 1 day 1 samples do not have to be repeated. Where applicable, cycle 1 day 8 and day 15 local labs must be obtained within 48 hours prior to dose (day 8 and day 15). Results must be** reviewed **prior to study drug administration**.
[e] **If screening local labs are** obtained within 72 hours prior **to cycle 1 day 1 dose, the pre-infusion cycle 1 day 1 samples do not have to be repeated. Results** must be reviewed **prior to study drug administration.**
[f] Imaging assessments must be within 21 days prior to the first dose of tarlatamab.
[g] Timing is based on first dose of tarlatamab (C1D1).

**Table 1-2. Schedule of Activities: Cycle 2+**

| **Procedure**[a] | **Treatment Period**[b] | | | | **EOT**[c] | **SFU**[d] | **LTFU**[e,f] | **As clinically indicated** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|
| | **Cycle 2** | | **Cycle 3+** | | | | | | |
| **Day** | **1** | **15** | **1** | **15** | | | | | |
| **GENERAL AND SAFETY ASSESSMENTS** | | | | | | | | | |
| Physical examination (including neurological exam) | **[X]** | X | **[X]** | X | X | X | | X | Physical exam must be completed prior to start of infusion on treatment days.<br>[X]: Must include weight on Day 1 of every cycle. |
| Vital Signs | X | X | X | X | X | X | | X | Includes systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature |
| ECOG PS | X | | X | | X | X | | | |
| ECG | | | | | **X** | | | X | |
| Adverse events | continuous | | | | | | | X | |
| Serious adverse events | continuous[g] | | | | | | | X | |
| Prior and Concomitant therapies review | continuous | | | | | | | X | |
| Survival Status | | | | | | | X | | |
| Subsequent anticancer therapy | | | | | X | X | X | | |
| **LABORATORY ASSESSMENTS** | | | | | | | | | |
| Pregnancy test (females of childbearing potential only)[h] | X | | X | | X | X | (X) | X | Serum or urine pregnancy test on Day 1 of every cycle should be collected.<br>(X): **60** days after the last dose of tarlatamab. |



Footnotes defined on last page of this table.

**Table 1-2. Schedule of Activities: Cycle 2+**

| Procedure[a] | Treatment Period[b] | | | | EOT[c] | SFU[d] | LTFU[e,f] | As clinically indicated | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | Cycle 2 | | Cycle 3+ | | | | | | |
| **Day** | **1** | **15** | **1** | **15** | | | | | |
| Coagulation[i] | X | X | X | | X | X | | X | |
| Hematology[i] | X | X | X | (X) | X | X | | X | (X): Cycle 3, 4, and 5 only. |
| Chemistry[i] | [X] | X | X | (X) | X | X | | X | [X]: Includes LDH and uric acid on C2D1 only.<br>(X): Cycle 3, 4, and 5 only. |
| Urinalysis | X | | (X) | | X | X | | X | (X): Collect on cycle 3, cycle 4 and then every other cycle (ie, cycle 6, 8, etc) on Day 1 only. |
| Lipase and amylase[j] | X | | X | | X | X | | X | |
| TSH and FT4[j] | | | | | X | | | X | |
| **CENTRAL LABORATORY ASSESSMENTS** | | | | | | | | | |
| PK sample[k] | X | | (X) | | | | | | All PK samples are collected pre-dose (ie, prior to start of tarlatamab infusion).<br>(X): Collect C3D1, C4D1, and then every other cycle (ie, cycle 6, cycle 8, etc) on Day 1 only.<br>PK samples to be collected up to cycle 12 only.<br>The time of dosing and PK sample collection should be accurately recorded. |
| Anti-tarlatamab antibody sample | X | | (X) | | X | X | | | All anti-tarlatamab antibody samples are collected pre-dose (ie, prior to start of tarlatamab infusion).<br>The time of dosing and anti-tarlatamab antibody sample collection should be accurately recorded.<br>(X): Collect C3D1, C4D1, and then every other cycle (ie, cycle 6, cycle 8, etc) on Day 1 only.<br>Anti-tarlatamab antibody samples are to be collected until EOT and SFU. |



Footnotes defined on last page of this table.

**Table 1-2. Schedule of Activities: Cycle 2+**

| Procedure[a] | Treatment Period[b] | | | | EOT[c] | SFU[d] | LTFU[e,f] | As clinically indicated | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | Cycle 2 | | Cycle 3+ | | | | | | |
| Day | 1 | 15 | 1 | 15 | | | | | |
| **IMAGING ASSESSMENTS** | | | | | | | | | |
| Radiological imaging and tumor assessment[k] | Weeks 1 to 48: Q6W (± 1 week) Weeks 49+ Q12W (± 1 week) by BICR per RECIST 1.1 | | | | (X) | (X) | [X] | X | Refer to Section **8.3.1** for additional details.<br>(X): For subjects who discontinued treatment for any reason other than radiographic PD, imaging is required at the EOT or SFU visit 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).<br>[X]: For subjects who discontinued treatment for any reason other than specified in Section 8.3.2, every effort should be made to perform scheduled radiographic imaging (CT/MRI) until radiographic progression. |
| **STUDY TREATMENT AND MONITORING** | | | | | | | | | |
| Tarlatamab Infusion[l] | X | X | X | X | | | | | |
| Monitoring post-tarlatamab infusion | | | | | | | | X | At subsequent visits, additional monitoring may be recommended post-tarlatamab infusion based on occurrence of CRS, ICANS, or ICANS-related neurological events. Refer to Table 6-1. |



Footnotes defined on last page of this table.

BICR = Blinded Independent Central Review; C1D1 = cycle 1 day 1; C2D1 = cycle 2 day 1; CRS = cytokine release syndrome; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion; EOT = end of treatment; FT4 = free T4; HIV = human immunodeficiency virus; ICANS = immune effector cell-associated neurotoxicity syndrome; LDH = Lactate dehydrogenase; LTFU = long-term follow-up; MUGA scan = multigated acquisition scan; PD = progressive disease; PK = pharmacokinetic; Q6W = every 6 weeks; Q12W = every 12 weeks; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SFU = safety follow-up; TSH = thyroid-stimulating hormone.

[a] All procedures and assessments on dosing days are to be completed prior to study drug administration unless otherwise indicated. Assessments should not be performed from the infusion line.

[b] Cycle 2 and all subsequent visits have a ± 3-day window, unless otherwise specified.

[c] Subjects who permanently discontinue treatment for any reason are encouraged to complete all remaining study visits and procedures through LTFU to ensure safety surveillance and/or collection of outcome data. Upon permanent discontinuation from tarlatamab treatment for any reasons, an EOT visit will be performed as soon as possible (within 14 days) after last dose of tarlatamab and prior to start of subsequent anticancer therapy.

[d] Safety follow-up visit will occur **60** (+ 5) days after the last dose of tarlatamab. Safety follow-up visits will occur regardless of initiation of subsequent anticancer therapy within that period.

[e] Assessed every 12 weeks (± 14 days) up to 1 year after the last subject's last dose of tarlatamab or 5 years from first subject enrolled, whichever occurs first. The study duration for subjects will be approximately up to 24 months, however this duration will be extended as needed to ensure all subjects have the opportunity to be followed in LTFU for at least 1 year after the last subject's last dose of tarlatamab.

[f] During LTFU, any serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen immediately and no later than 24 hours of awareness.

[g] After end of study, serious adverse events suspected to be related to investigational product will be reported to Amgen. Please refer to Section 8.4.6.4 for additional details.

[h] 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

[i] Local **labs** must be obtained within 48 hours prior to dose on dosing days for tarlatamab. Laboratory results must be reviewed prior to study drug administration.

[j] Labs must be obtained within 72 hours prior **to dose on dosing days for tarlatamab** and must be reviewed by the investigator before each dose. If labs are to be obtained more than 72 hours before the dose, prior approval by the medical monitor is required.

[k] Timing is based on first dose of tarlatamab (C1D1).

[l] For information on tarlatamab treatment beyond progression, refer to Section 6.1.7. Subjects who continue on treatment should follow assessments as shown in the Schedule of Activities.

# 2. Introduction

## 2.1 Study Rationale

Small cell lung cancer (SCLC) is a grave diagnosis, marked by high initial response rates to platinum-based first-line chemotherapy. However, resistance to subsequent treatments quickly emerges, resulting in a median survival of 10 to 12 months post-diagnosis (Rudin et al, 2015). Delta-like ligand 3 (DLL3) is typically intracellular in normal tissues but often overexpressed on the cell surface in most SCLC tumors, making it an attractive target for T-cell therapies (Saunders et al, 2015). Notably, minimal cytoplasmic staining is observed in the brain, pituitary, and pancreatic islets in normal tissues (Study 123377), suggesting the potential for tumor-specific DLL3-targeted therapy.

Tarlatamab (INN; AMG 757) is a novel, extended half-life (HLE) bispecific T-cell engager (BiTE®) designed to direct T effector cells toward DLL3-expressing cells using a tandem single-chain fragment crystallizable (scFc) for prolonged half-life. In an ongoing phase 2 study (Study 20200491), tarlatamab has demonstrated efficacy in SCLC patients with a manageable safety profile (Ahn et al, 2023).

**Tarlatamab received accelerated approval from the United States Food and Drug Administration (FDA) for the treatment of adult patients with extensive-stage SCLC with disease progression on or after platinum-based chemotherapy.**

Study 20230273 aims to assess tarlatamab's efficacy, safety, tolerability, and pharmacokinetics (PK) in Chinese subjects with advanced SCLC who have progressed on or recurred following 1 platinum-based regimen as first-line (1L) therapy (including a Programmed Cell Death Protein 1 [PD-1]/Programmed Cell Death Ligand 1 [PD-1/PD-(L)1]) and at least 1 other prior line of therapy (re-treatment with a platinum-based regimen is considered a second-line of therapy).

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

## 2.2 Background

### 2.2.1 Disease

Small cell lung cancer accounts for 10 to 15% of lung cancer (Rudin et al, 2015), presenting as an aggressive subtype with neuroendocrine differentiation, strongly linked to smoking (Koinis et al, 2016). It exhibits distinct characteristics, including a high

growth rate, rapid doubling time, and early widespread metastasis (Gustafsson et al, 2008).

Approximately 30% of patients have limited disease (LD) confined to one hemithorax, while the majority have extensive disease (ED). Small cell lung cancer is highly responsive to first-line chemotherapy (60% to 70% response rates) and radiation, but resistance rapidly develops for second-line and subsequent therapies after disease recurrence (Byers and Rudin, 2015).

Patients with ED face drug resistance and typically succumb to the disease within a median time of 10 to 12 months from diagnosis (Rudin et al, 2015). First-line treatment for ED-SCLC involves platinum-based chemotherapy, such as platinum etoposide (EP) or platinum irinotecan. Anlotinib is an orally administered tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptors (PDGFR), and c-kit. It is used in China as the current recommended treatment in third or later line treatment in advanced SCLC, based on the evidence in ALTER1202. This study demonstrates a significant improvement in median progression-free survival (PFS) and a consistent trend in overall survival (OS) (4.0 vs 0.7 months, $P < 0.0001$)/(7.3 vs 4.4 months, $P = 0.006$, respectively) compared with placebo (Shi et al, 2020). However, it shows numerically limited improvements in response rate (objective response rate [ORR] of 4.9%). A median OS of 6.86 months was observed through a real-world study which includes 13 studies, involving 779 patients with SCLC (Xu et al, 2023). There are no approved third-line therapies for relapsed ED-SCLC outside of China, and existing options offer limited OS benefits, with a median OS of 4.4 months (Coutinho et al, 2019). Therefore, there remains a critical medical need for new therapies in third and later-line settings.

### 2.2.2 Amgen Investigational Product Background: Tarlatamab

BiTE® molecules guide T effector memory cells toward target cells, closely mimicking cytotoxic T lymphocyte activation. Tarlatamab, an HLE BiTE®, combines binding specificities for DLL3 and CD3, genetically fused to the N terminus of the immunoglobulin G scFc region. It is being developed to treat SCLC patients, with its activity dependent on binding to both target cells and T cells. Tarlatamab redirects primed cytotoxic $CD8^+$ or $CD4^+$ T lymphocytes to eliminate $DLL3^+$ cells.

**In the phase 1 first in human study (Study 20160323) evaluating the safety, tolerability, and antitumor activity of tarlatamab in SCLC, the available data demonstrate that tarlatamab shows a manageable safety profile and signs of preliminary efficacy.**

**The pivotal phase 2 study of tarlatamab in patients with relapsed SCLC after 2 lines of prior therapy has confirmed efficacy and benefit/risk ratio (Study 20200491; Ahn et al, 2023). Based on a pre-specified interim analysis in part 1 of the phase 2 Study 20200491, the regimen using a 10 mg target dose Q2W with a 1 mg step-dose was selected as the monotherapy recommended phase 2 dose 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.**

**Tarlatamab received accelerated approval from the United States FDA for the treatment of adult patients with extensive-stage SCLC with disease progression on or after platinum-based chemotherapy; please refer to the United States Prescribing Information.**

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

### 2.2.3 Non-Amgen Investigational Product Background

No non-Amgen investigational products will be used in this study.

## 2.3 Benefit/Risk Assessment

Delta-like ligand 3 is a promising T-cell therapy target is highly expressed in SCLC and other neuroendocrine tumors but minimally expressed in normal tissues. Tarlatamab demonstrated potent T-cell recruitment against DLL3-expressing SCLC cells in vitro and effectively suppressed tumor growth in systemically treated mice. Tarlatamab is expected to offer deeper and more durable responses compared to current and emerging treatments for SCLC.

As of 27 June 2023 (Study 20200491), among patients evaluated for antitumor activity and survival, the median follow-up was 10.6 months in the 10 mg group. An objective response occurred in 40% (97.5% CI, 29 to 52) of the patients. Among patients with an objective response, the duration of response was at least 6 months in 59% (40 of 68 patients). Objective responses at the time of data cutoff were ongoing in 22 of

40 patients (55%) and the median progression-free survival was 4.9 months (95% CI, 2.9 to 6.7); the estimates of OS at 9 months were 68% (Ahn et al, 2023).

**Key Safety Information**

Based on tarlatamab's ongoing clinical study experience, the key safety information includes the adverse drug reactions of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and neutropenia. Additionally, potential safety issues includes pituitary dysfunction, other neurological events, and tumor lysis syndrome (TLS) which stem from Tarlatamab's mechanism of action and experience with BiTE® molecules. For complete details, consult the investigator's brochure.

A comprehensive safety strategy, focusing on CRS, ICANS, neutropenia, other neurological toxicities, pituitary dysfunction, and TLS will be implemented in this study. This includes prevention, continuous monitoring, early recognition, and prompt management. See Section 6.2.2 and Table 6-2 for detailed management recommendations **of the key adverse drug reactions and potential safety concerns of tarlatamab**.

The above benefit-risk assessment supports the conduct of this clinical study.

For additional details on the safety risks, refer to the investigator's brochure.

## 3. Objective(s) and Endpoint(s)/Estimand(s)

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • Evaluate efficacy of tarlatamab as assessed by objective response rate (ORR) based on blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) | • ORR BICR, defined as proportion with best overall response (BOR) of complete response (CR) plus partial response (PR) |
| **Secondary** | |
| • Evaluate efficacy of Tarlatamab as assessed by duration of response (DOR), disease control (DC), and progression-free survival (PFS) based on BICR per RECIST 1.1 | • DOR, defined as time from the first documentation of objective response (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<br>• DC, defined as CR + PR + stable disease (SD)<br>• Duration of DC, defined as time from the first documentation of CR, PR, or SD until the first documentation of disease progression or death due to any cause, whichever occurs first. Only subjects who have achieved CR, PR, or SD will be evaluated for Duration of DC<br>• PFS, defined as time from enrollment until disease progression or death from any cause, whichever occurs first. Progression will be based on RECIST 1.1. |
| • Evaluate efficacy of Tarlatamab as assessed by ORR, DOR, DC, and PFS based on investigator assessment per RECIST 1.1 | • ORR (Investigator)<br>• DOR<br>• DC<br>• Duration of DC<br>• PFS |
| • Evaluate efficacy of Tarlatamab as assessed by overall survival (OS) | • OS, defined as time from enrollment until death from any cause |
| • Evaluate safety and tolerability | • Incidence of treatment-emergent adverse events |
| • Characterize the pharmacokinetics of tarlatamab | • Serum concentration of tarlatamab |

| | |
|---|---|
| • Evaluate the immunogenicity of tarlatamab | • Incidence of anti-tarlatamab antibody formation |

**Estimand(s) for Primary Objective(s)**

Objective response rate (ORR) by blinded independent central review (BICR) per RECIST 1.1 in Chinese subjects with advanced SCLC who have progressed on or recurred following 1 platinum-based regimen as 1L therapy (including a PD-1/ PD [L]1) and at least 1 other prior line of therapy (re treatment with a platinum-based regimen is considered a second line of therapy) prior to start of new cancer therapy (while-on-treatment strategy).

## 4. Study Design

### 4.1 Overall Design

This is a phase 2a, multicenter, single arm, open-label study in Chinese subjects with advanced SCLC who have progressed on or recurred following 1 platinum-based regimen as 1L therapy (including a PD-1/PD-[L]1) and at least 1 other prior line of therapy (re-treatment with a platinum-based regimen is considered a second-line of therapy).

Approximately 30 Chinese subjects are planned to be enrolled in the study.

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

Study treatment will be administered as follows:

- Tarlatamab will be administered as a 60-minute (± 10 minutes) intravenous (IV) infusion with 1 mg step dose on cycle 1 day 1 (C1D1) followed by a 10 mg target dose on cycle 1 day 8 (C1D8), and cycle 1 day 15 (C1D15) in a 28-day cycle. Subsequent doses (10 mg) will be administered every 2 weeks (Q2W) (ie, cycle 2+ day 1/day 15 dosing) in a 28-day cycle.
- Monitoring during cycle 1:
  - 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 (C1D2) and cycle 1 day 9 (C1D9) 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 dose of other corticosteroids) will be administered within 1 hour prior to tarlatamab infusion on C1D1 and C1D8.
- Intravenous Hydration: 1 L normal saline over 2 to 4 hours following tarlatamab administration on C1D1 and C1D8.

Subjects will receive study treatment until BICR-**confirmed** disease progression per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), death, withdrawal of consent, start of new anticancer therapy, unacceptable toxicity, 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. Any subsequent (investigator determined) progressive disease per RECIST 1.1 from a new baseline set at initial progression will result in permanent discontinuation of study treatment.

**The site principal investigator will make final treatment and subject management decisions. Subjects who discontinue study treatment for reasons other than BICR-confirmed disease progression will continue to have tumor assessments (if clinically feasible) until disease progression is confirmed by BICR**.

A SFU visit will occur **60** (+ 5) days after the last dose of tarlatamab regardless of initiation of subsequent anticancer therapy within that period. After the SFU visit, subjects will be followed in LTFU for survival every 12 weeks (± 14 days) for up to 1 year after the **last** subject's last dose of tarlatamab or 5 years from first subject enrolled, whichever is first.

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

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

### 4.2 Patient Input into the Study Design

Patient input was not obtained for this study.

### 4.3 Justification for Dose

#### 4.3.1 Justification for Investigational Product Dose

The study will evaluate tarlatamab at a 10 mg target dose on a Q2W regimen which is the recommended Phase 2 dose of tarlatamab and for all ongoing studies **and is an approved regimen in the United States, under an accelerated approval by the FDA**. To mitigate CRS risk, treatment will begin with a 1 mg step dose on C1D1, followed by the 10 mg target dose on C1D8, C1D15, and Q2W thereafter, each infusion

administered over 60 minutes. This regimen was selected based on data from the first-in-human Study 20160323, which explored a target dose range of 0.003 to 100 mg on a Q2W regimen in SCLC patients, as well as findings from the ongoing phase 2 Study 20200491, which evaluated active dose levels of 10 and 100 mg on a Q2W schedule using a 1 mg step dose.

The planned dosing regimen of 10 mg Q2W exhibited near maximal efficacy and favorable benefit-risk profile in SCLC patient population (Ahn et al, 2023; Paz-Ares et al, 2023).

For the latest efficacy and safety data from ongoing studies, please refer to the investigator's brochure.

### 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 **6 to 8 hours** monitoring following the first two tarlatamab doses (cycle 1 day 1 and day 8) and leveraging additional risk mitigation measures: mandatory counseling on signs and symptoms of CRS at time of discharge, a cohabitant for first 24 hours after cycle 1 day 1 and day 8 infusions, and remaining within 1 hour of an appropriate healthcare setting after cycle 1 day 1 and day 8 infusions. Importantly, patients will return to study sites on the day following these infusions for clinical evaluation (ie, cycle 1 day 2 and cycle 1 day 9). 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

Individual subject study completion is determined by completing the last visit in the Schedule of Activities (See Section 1.3). The study duration for each subject includes up to 21 days for screening, followed by a variable treatment **period, and** there is a SFU of **60** (+ 5) days after the last tarlatamab dose, and a LTFU that spans up to 1 year after the last subject's last dose of tarlatamab or 5 years from first subject enrolled, whichever is first. **The study duration for subjects will be approximately up to 24 months, however, this duration will be extended as needed to ensure all subjects have the**

**opportunity to be followed in LTFU for at least 1 year after the last subject's last dose of tarlatamab.**

## 5. Study Population

Investigators will be expected to maintain a screening log to record details of all subjects screened that includes limited information about the screened subject (eg, date of screening). This log may be completed and updated via an Interactive Response Technology (IRT).

Eligibility criteria will be evaluated during screening.

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

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

### 5.1 Inclusion Criteria

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

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

102 Subjects must be a resident in China, and of Chinese ancestry ≥ 18 years of age (or legal adult age within country) at the time of signing the informed consent.

103 Histologically or cytologically confirmed SCLC.

104 **Extensive-stage SCLC s**ubjects who progressed on or recurred following 1 platinum-based regimen as 1L therapy (including a PD-1/ PD-[L]1) and at least 1 other prior line of therapy.

Note: (1) re-treatment with a platinum-based regimen is considered a second-line of therapy; (2) platinum-based regimen followed by checkpoint inhibitor/anti-PD-L1 as maintenance therapy is considered 1 line of therapy.

105 Measurable lesions as defined per RECIST 1.1 within 21 days prior to the first dose of tarlatamab.

- Screening scans performed as standard of care (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**.

106 Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

107 Minimum life expectancy of 12 weeks.

108 Adequate organ function, defined as follows:

- hematological function:
  - absolute neutrophil count $\geq 1 \times 10^9$/L
  - platelet count $\geq 100 \times 10^9$/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) $\leq$ 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. Subjects on chronic anticoagulation therapy who do not meet the criteria above may be eligible to enroll after discussion with the medical monitor.
- 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), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) < 3 x ULN (or < 5 x ULN for subjects with liver involvement)
  - total bilirubin < 1.5 x ULN (or < 2 x ULN for subjects with liver metastases)
- 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**

201 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.

202 Symptomatic CNS metastases:

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

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

203 Diagnosis or evidence of leptomeningeal disease.

204 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**

205 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.

206 History of solid organ transplantation.

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

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

- malignancy treated with curative intent and with no known active disease present for ≥ 1 year before enrollment and believed to be at low risk for recurrence by the treating physician
- adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- adequately treated cervical carcinoma in situ without evidence of disease
- adequately treated breast ductal carcinoma in situ without evidence of disease
- prostatic intraepithelial neoplasia without evidence of prostate cancer
- adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

209 Myocardial infarction and/or symptomatic congestive heart failure (New York Heart Association > class II) within 12 months of first dose of tarlatamab (Section 11.9).

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

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 tarlatamab.

- 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 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 are not required unless otherwise noted as exclusion criteria.

212 HIV, Hepatitis B, and Hepatitis C.

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 antibody [HCV Ab positive] 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-positive] and HBV DNA viral load above the limit of quantification [HBV DNA positive]).

- Subjects with resolved hepatitis B virus (HBV) infection, defined as absence of HBV surface antigen [HBsAg-negative] and presence of HBV core antibody [anti-HBc positive] 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 hepatitis B virus (HBV) infection inactive carrier state, defined as presence of HBV surface antigen [HBsAg-positive] 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.

213 Major surgery within 28 days of first dose tarlatamab.

**Prior/Concomitant Therapy**

214 **Currently or previously enrolled in a** tarlatamab **study**.

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

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 $\leq$ 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 tarlatamab.

217 Receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of tarlatamab.

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

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

**Prior/Concurrent Clinical Study Experience**

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

**Other Exclusions**

220 Female subjects of childbearing potential unwilling to use protocol-specified method of contraception (see Section 11.5) during treatment and for an additional **60** days after the last dose of tarlatamab.

221 Female subjects who are breastfeeding or who plan to breastfeed while on study through **60** days after the last dose of tarlatamab.

222 Female subjects planning to become pregnant or donate eggs while on study through **60** days after the last dose of tarlatamab.

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

224 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 Section 11.5 for additional contraceptive information.

225 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.

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

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

228 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.

229 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 medical monitor if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

### 5.3 Lifestyle Considerations

No lifestyle considerations are applicable to the conduct of this study.

### 5.4 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written external review bodies (eg, the institutional review board [IRB]/independent ethics committee[IEC]/regulatory authorities) 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 and the investigator or authorized delegate must personally sign and date the external review body informed consent before commencement of study-specific procedures.

Each subject who enters the screening period for the study (defined as the point at which the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned using 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.

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 first dose of investigational product administration. 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.

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

## 5.5 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. 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), or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that according to local regulations in some countries, investigational product(s) described in Section 6.1.1 are referred to as investigational medicinal product(s) and noninvestigational product(s)/auxiliary medicinal product(s) described in Section 6.1.2 are referred to as noninvestigational medicinal product(s).

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

## 6.1 Study Interventions Administered

### 6.1.1 Investigational Products

## Table 6-1. Investigational Products

| Study Treatment Name | Amgen Investigational Product:[a] Tarlatamab (AMG 757) |
|---|---|
| **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. |
| **Dosage Level(s)** | 1 mg step dose on C1D1<br>10 mg target dose starting C1D8, C1D15, and Q2W thereafter |
| **Route of Administration** | IV infusion |
| **Accountability** | Product administration information is 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.

**Table 6-1. Investigational Products**

| | |
|---|---|
| **Monitoring Guidance** | • Cycle 1 Day 1 and Cycle 1 Day 8:<br>  ○ 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.<br>  ○ 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 the signs and symptoms of CRS and ICANS by a healthcare provider is required prior to discharge.<br>• Subjects return to site on cycle 1 day 2 and cycle 1 and day 9 for vital signs and physical examination.<br>• 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).<br>  – Refer to the C1D1 requirements above.<br>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. |

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C1D1 = cycle 1 day 1; C1D8 = cycle 1 day 8; C1D15 = cycle 1 day 15; CRS = cytokine release syndrome; eCRF = electronic case report form; ICANS = immune effector cell-associated neurotoxicity syndrome; IV = intravenous; 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.

### 6.1.2 Noninvestigational Products/Auxiliary Medicinal Products

After the occurrence of an event that, in the opinion of the investigator, warrants other treatment, supportive care should be provided including, but not limited to, the guidance in Table 6-2 for Dose Modification Guidelines for Adverse Events.

#### 6.1.2.1 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 C1D1 and C1D8.

**IV Hydration**

Intravenous hydration (1 L normal saline) over 2 to 4 hours following tarlatamab administration on C1D1 and C1D8.

#### 6.1.2.2 Cytokine Release Syndrome Rescue Medication

All sites will ensure that CRS rescue medications are available on-site, including corticosteroids and sites are required to have tocilizumab or siltuximab (if tocilizumab is not available) on site for potential treatment of CRS.

### 6.1.3 Medical Devices

Non-investigational 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 or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

### 6.1.4 Other 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 product and/or other non-investigational product(s)/auxiliary medicinal product(s)provisioned and/or repackaged/modified by Amgen:

- tarlatamab

Any product complaint(s) associated with an investigational product and/or noninvestigational product(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 mpox 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 coronavirus disease 2019 ([COVID-19], severe acute respiratory syndrome coronavirus 2 [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** ($+5$) days after the last dose of tarlatamab.
- Subjects must not schedule any major elective surgery during the treatment period and for at least 30 days after the last administration of study treatment. If a subject undergoes any unexpected surgery during the course of the study, all study

treatments must be withheld, and the investigator or designee should notify the sponsor's medical monitor as soon as possible. A subject may be allowed to resume study drugs if both the investigator and sponsor's medical monitor agree to restart study therapy.

### 6.1.7 Continuation on Investigational Product Treatment After First Radiologic Disease Progression

This section details the conditions necessary to allow continued study treatment 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 of brain metastases 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 11.7.1**).
- 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.
- Radiation therapy is permitted after discussion with the medical monitor. 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 should continue to perform all protocol-required procedures as noted in the Schedule of Activities (Section 1.3; imaging, labs, and clinic visits).

Any subsequent (investigator determined) progressive disease per RECIST 1.1 from a new baseline set at initial progression will result in permanent discontinuation of study treatment.

## 6.2 Dose Modification

### 6.2.1 Dose-group 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 dose change of tarlatamab is to be recorded on each subject's CRF(s).

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 delay. 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:<br>• Consider diagnostic workup for alternate diagnosis[a]<br>• Supportive Care | No additional guidance | No additional guidance |
| 2 | | No additional guidance | Follow institutional guidelines for management and administer corticosteroids per local practice:<br>• Consider diagnostic workup for alternate diagnosis[a]<br>Reference dose of corticosteroids for grade 2 ICANS[a]:<br>• 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:<br>• Consider diagnostic workup for alternate diagnosis[a]<br>• Consider ICU transfer<br>Reference dose of corticosteroids for grade 3 ICANS[a]:<br>• 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<br>• 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 (continued)** | | | | | |
| 4 | Reference Section 11.11.2 for grading and management guidelines | Immediately stop any ongoing infusion | Follow institutional guidelines for management and administer corticosteroids per local practice:<br>• Consider diagnostic workup for alternate diagnosis[a]<br>• Transfer to ICU<br>Reference dose of corticosteroids for grade 4 ICANS[a]:<br>• 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 | | Delay tarlatamab until the event improves to grade ≤ 1 | 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[b] | 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<br>• Fever[c]: ≥ 38°C<br>• Hypotension: none<br>• Hypoxia: none | No action required | Administer:<br>• Symptomatic treatment (eg, paracetamol/acetaminophen) for fever<br>• Consider a single dose of dexamethasone (or equivalent) ranging from 4 mg to 10 mg<br>Monitor:<br>• CRS symptoms including temperature, blood pressure, and pulse oximetry<br>• Fluid status, maintain IVF as needed<br>• Consider chest X-ray and obtaining appropriate cultures to rule out infection<br>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. | 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[b] | 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[c]: ≥ 38°C<br>WITH<br>• Hypotension: not requiring vasopressors<br>AND/OR[d]<br>• Hypoxia: requiring low-flow nasal cannula[e] or blow-by | Delay tarlatamab until event improves to CRS grade ≤ 1. | Administer:<br>• Symptomatic treatment (eg, paracetamol/acetaminophen) for fever<br>• Consider a single dose of dexamethasone (or equivalent) ranging from 4 mg to 10 mg<br>• Supplemental oxygen when oxygen saturation is < 90% on room air (low-flow [≤ 6 L/minute] nasal cannula or blow-by)<br>• Intravenous fluids when systolic blood pressure is < 85 mmHg. Persistent tachycardia (eg, > 120 bpm) may also indicate the need for intervention for hypotension<br>Monitor:<br>• CRS symptoms including temperature, blood pressure, and pulse oximetry<br>• Fluid status, maintain IVF as needed<br>• Cardiac and other organ function<br>• Consider chest X-ray and obtaining appropriate cultures to rule out infection<br>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. | • The next infusion may be administered if the event has resolved to grade ≤ 1 prior to resuming treatment<br>• 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 1 within 7 days |



Abbreviations and footnotes defined on last page of table.

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

| Grade | Description of Severity[b] | 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[c]: ≥ 38°C<br>WITH<br>• Hypotension: requiring a single vasopressor (excluding vasopressin)<br>AND/OR[d]<br>• Hypoxia: requiring high-flow nasal cannula[e], facemask, nonrebreather mask, or Venturi mask | Delay tarlatamab until event improves to CRS grade ≤ 1. | Administer:<br>• Symptomatic treatment (eg, paracetamol/acetaminophen) for fever<br>• Supplemental oxygen (high-flow nasal cannula [> 6 L/min]), facemask, non-rebreather mask, or Venturi mask), as needed<br>• A vasopressor ± vasopressin, as needed<br>• 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.<br>AND/OR<br>• Consider use of tocilizumab (in countries where available) as an additional therapy in this setting at a dose of 4 to 8 mg/kg as a single dose. **The maximum dose per infusion for tocilizumab is 800 mg**. Tocilizumab can be repeated for an additional 3 doses with at least an 8-hour interval between doses.<br>• 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.<br>• As per local institutional guidelines. | The next infusion may be administered if all of the following criteria are met:<br>• The medical monitor must be consulted prior to resuming treatment<br>• The event has resolved to grade ≤ 1 prior to resuming treatment<br>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.<br>OR<br>If CRS grade 3 occurs at the step dose.<br>OR<br>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[b] | 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:<br>• CRS symptoms including temperature, blood pressure, and pulse oximetry<br>• Fluid status, maintain IVF as needed<br>• Consider chest X-ray and obtaining appropriate cultures to rule out infection<br>• If refractory hypotension (after 2 fluid boluses), consider ECHO<br>Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines | | |
| 4 | Life-threatening symptoms<br>• Fever[c]: ≥ 38°C<br>WITH<br>• Hypotension: requiring multiple vasopressors (excluding vasopressin)<br>AND/OR[d]<br>• Hypoxia: requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) | Immediately stop any ongoing infusion | Administer:<br>• Symptomatic treatment (eg, paracetamol/acetaminophen) for fever<br>• Supplemental oxygen (positive pressure [eg, CPAP, BiPAP, intubation, and mechanical ventilation], as needed)<br>• Multiple vasopressors, as needed<br>• 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 medical monitor.<br>• Tocilizumab should be administered at a dose of 4 to 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 |



Abbreviations and footnotes defined on last page of table.

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

| Grade | Description of Severity[b] | 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.<br>Monitor:<br>• CRS symptoms including temperature, blood pressure, and pulse oximetry<br>• Fluid status, maintain IVF as needed<br>• Consider chest X-ray and obtaining appropriate cultures to rule out infection<br>• If refractory hypotension (after 2 fluid boluses), consider ECHO<br>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) (see Section 11.11.3)** | | | | |
| Present | Immediate interruption/delay until event has resolved | TLS should be managed according to the local standard of care and institutional guidelines. | • Resume only if TLS is successfully managed and resolved in ≤ 14 days<br>• Consult with medical monitor first.<br>• In case of infusion interruption, continue treatment with next scheduled infusion. Do not resume prior infusion or administer delayed infusion.<br>• Monitoring: per Monitoring Guidance for first tarlatamab administration (Section 6.1) | If subject missed more than 2 consecutive doses of tarlatamab<br>OR<br>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[f] | Delay tarlatamab until the event improves to grade ≤ 2 | • Assess for other potential etiologies of neutropenia, including concomitant medications and underlying infection<br>• Consider bone marrow biopsy, anti-neutrophil antibodies<br>• 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[f] | Delay tarlatamab until the event improves to grade ≤ 2 | • Assess for other potential etiologies of neutropenia, including concomitant medications and underlying infection<br>• Consider bone marrow biopsy, anti-neutrophil antibodies<br>• Consider G-CSF administration | Resume tarlatamab no less than 72 hours after the initial observation of the grade 4 adverse event | Initial grade 4 nonfebrile neutropenia event lasts > 7 days<br>OR<br>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**

| Grade | Description of Severity | Interruption/Delay | Specific Management | Restart Guidance | Permanent Discontinuation |
|---|---|---|---|---|---|
| **Hypersensitivity (Allergic Reactions)** | | | | | |
| **1** | **Systemic intervention not indicated** | **No additional guidance** | **Follow institutional guidelines for management** | **No additional guidance** | **No additional guidance** |
| **2** | **Oral intervention indicated** | **Immediately pause any ongoing infusion** | **Follow institutional guidelines for management and administer oral antihistamines and/or corticosteroids per local practice.** | **Restart current infusion of remaining dose at lower rate per local practice if event has resolved** | **No additional guidance** |
| **3** | **Bronchospasm, hospitalization indicated for clinical sequelae; intravenous intervention indicated** | **Immediately stop any ongoing infusion and do not resume the current infusion.**<br><br>**Delay next tarlatamab administration until the event improves to grade ≤ 1** | **Follow institutional guidelines for management and administer IV corticosteroids, antihistamines, IV fluids, supplemental oxygen, and consider epinephrine per local practice**<br>**Close monitoring**<br>**and**<br>**Consider ICU transfer** | **The next infusion may be administered if**<br>**all the following criteria are met:**<br>• **The Amgen medical monitor must be consulted prior to resuming treatment**<br>• **The event has resolved to grade ≤ 1 prior to resuming treatment**<br>• **Consider premedication (ie, antihistamine, corticosteroid) prior to the next infusion** | **Discontinue tarlatamab if:**<br>**there is no improvement to**<br>**≤ grade 1 within 5 days**<br>**OR**<br>**if grade 3 occurs at the step dose**<br>**OR**<br>**in the case of 2 separate grade 3 events.** |



**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 |
|---|---|---|---|---|---|
| **Hypersensitivity (Allergic Reactions) continued** | | | | | |
| **4** | **Life-threatening consequences, urgent intervention indicated** | **Immediately stop any ongoing infusion and do not resume the current infusion.** | **Follow institutional guidelines for management and administer epinephrine, IV corticosteroids, antihistamines, IV fluids, and supplemental oxygen per local practice.**<br>**Immediate medical attention, ICU care, intubation as clinically indicated.** | **Do not resume tarlatamab.** | **Permanently discontinue tarlatamab** |



**Abbreviations and footnotes defined on last page of table.**

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

| **Pituitary Gland Dysfunction (González-Rodríguez and Rodríguez-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<br>– Abnormal hormone monitoring result or clinical suspicion of pituitary gland dysfunction (headache, fatigue, asthenia, impaired vision, vomiting, hypotension, amenorrhea, impotence)<br>– 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)<br>• Urgent endocrinology consultation to guide management of the event<br>• Once pituitary gland dysfunction is confirmed, delay scheduled dose of tarlatamab<br>• Once residual related toxicity ≤ grade 2, clinically stable on replacement therapy and < 10 mg prednisone or equivalent, resume tarlatamab<br>• 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; ECHO = echocardiogram; FSH = follicle-stimulating hormone; FT4 = free T4; G-CSF = granulocyte colony-stimulating factor; ICANS = immune effector cell-associated neurologic syndrome; IGF-1 = insulin-like growth factor 1; IL-6 = interleukin 6; IV = intravenous; IVF = intravenous fluid(s); LH = luteinizing hormone; MRI = magnetic resonance imaging; OS = overall survival; PS = performance status; TLS = tumor lysis syndrome; TSH = thyroid-stimulating hormone

[a] Based on Immune Effector Cells 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

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

[c] 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.

[d] 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.

[e] 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.

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

For all other treatment interruptions or delays, restart 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 10 mg target dose and then continue treatment Q2W. |
| | > 14 days | Repeat tarlatamab 1 mg 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 10 mg target dose and then continue treatment Q2W. |
| | > 21 days | Repeat tarlatamab 1 mg step dose schedule per cycle 1 guidelines, including pre-medication and monitoring requirements (refer to ). |
| **Any subsequent target dose (10 mg)** | ≤ 28 days | Proceed with tarlatamab 10 mg target dose and then continue treatment Q2W. |
| | > 28 days | Repeat tarlatamab 1 mg step dose per cycle 1 guidelines, including pre-medication and monitoring requirements (refer to Table 6-1). |

Q2W = every 2 weeks.

### 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 preparation, handling, storage, and accountability for the investigational product, and noninvestigational product(s)/auxiliary medicinal product(s) will be provided to the site.

## 6.4 Method of Treatment Assignment

Subjects who meet eligibility criteria and enroll in the study will be assigned to treatment with tarlatamab.

## 6.5 Blinding

This is an open-label study; procedures to blind treatment assignment are not applicable.

## 6.6 Treatment Compliance

When subjects are dosed at the site, they will receive tarlatamab 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.

## 6.7 Treatment of Overdose

The effects of overdose of tarlatamab are not known.

For this study, any dose of tarlatamab greater than 10% of intended dose will be considered an overdose. A dose of greater than 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”.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor immediately for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage. Consultation with the medical monitor is also required even if there are no adverse events, to discuss further management of the subject.
2. If the overdose results in clinically apparent or symptomatic adverse events, closely monitor the subjects until all signs or toxicity are resolved or returned to

baseline and the adverse event(s) should be recorded/reported (refer to Section 11.4, Appendix 4).

3. Document the quantity of the excess dose in the CRF.

## 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 on each subject's CRF.

### 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 6.1.6.

Concomitant therapies (including prescription and non-prescription, herbal, and alternative therapies) are to be collected from main study informed consent through the end of the SFU period.

**Vaccines**

Refer to Section 6.1.6 for details on the use of vaccines.

# 7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Subjects have the right to withdraw from investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), and/or 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(s), noninvestigational product(s)/auxiliary medicinal product(s), device, and/or protocol procedures, or the study as a whole at any time before 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(s) and/or noninvestigational product(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(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and must discuss with the subject the

possibilities for continuation of the Schedule of Activities (see Section 1.3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and 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(s) and/or noninvestigational product(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. **Continuation on investigational product treatment may be allowed after first radiologic disease progression, see Section 6.1.7**.

Reasons for early removal from investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s) and/or procedures 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 **(see Section 6.1.7)**
- 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, or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study and must document the subject's decision to withdraw in the subject's medical records. 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 the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, where permitted per local regulation, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods [contact the patient's family or direct assigned contact]). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, 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 survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

# 8. Study Assessments and Procedures

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

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

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

## 8.1 General Study Periods

### 8.1.1 Screening and Enrollment

Informed consent must be obtained before completing any screening procedure. After the subject has signed the informed consent form, the site will register the subject in IRT and screen the subject to assess eligibility for participation. The screening window is up to 21 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.5) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening up to 2 additional times.

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

### 8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 1.3). The date of the first dose of tarlatamab is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. On-study cycle 1 day 8 and day 15 visits have a ± 1 day window and all subsequent visits beginning from cycle 2 have a ± 3 day window, unless otherwise specified. Administration of tarlatamab is to be administered last during each visit that it is required. **Subjects will receive study treatment until BICR-confirmed disease progression per RECIST 1.1, death, withdrawal of consent, start of new anticancer therapy, unacceptable toxicity, 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. Any subsequent (investigator-determined) progressive**

**disease per RECIST 1.1 from a new baseline set at initial progression will result in permanent discontinuation of study treatment.**

**The site principal investigator will make final treatment and subject management decisions. Subjects who discontinue study treatment for reasons other than BICR-confirmed disease progression will continue to have tumor assessments (if clinically feasible) until disease progression is confirmed by BICR.**

### 8.1.3 End of Treatment

**Upon permanent discontinuation from study treatment for any reason, an end of treatment visit will be performed at the time the decision is made to discontinue study treatment (preferably within 14 days after last dose of study treatment) and prior to the start of subsequent anti-cancer therapy.**

### 8.1.4 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately **60** (+5) days after the end of the last dose of tarlatamab, regardless of initiation of subsequent anticancer therapy within that period.

### 8.1.5 Long-term Follow-up

Following the SFU visit (**60** [+5] days), subjects will enter the 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 1 year after the last subject's last dose of tarlatamab or 5 years from first subject enrolled, whichever occurs first. Radiological imaging and pregnancy testing may also be collected during the LTFU period, if applicable. 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 will occur during the LTFU.

All end of study procedures should be performed at the final visit for subjects who discontinue study before the defined end of study visit. Amgen will not continue provision of investigational product for subjects after their study participation ends unless it is a legal requirement.

## 8.2 General Assessments

### 8.2.1 Informed Consent

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

### 8.2.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on the PK of tarlatamab.

### 8.2.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started prior to enrollment through the time of first dose. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, SCLC history must date back to the original diagnosis.

### 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).

At minimum, the examination should include assessments of the head and neck, skin, neurological, lungs, cardiovascular, abdomen (liver and spleen), thyroid, lymph nodes, and extremities.

### 8.2.5 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 electronic Case Report Form (eCRF). Abnormal findings found after the subject is dosed will be reported on the Event page of the eCRF.

### 8.2.6 Physical Measurements

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

### 8.2.7 Performance Status

The subject's performance status 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.

Screening scans:

The screening scans must be performed within 21 days prior to enrollment. If there are multiple screening scans, the one closest to the enrollment will be used as baseline. Assessments that were performed as SOC prior to signature of informed consent, but within 21 days prior to first dose of tarlatamab 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 imaging of the brain performed within 21 days prior to the first dose of tarlatamab. All brain scans for subjects are required to be MRI unless MRI is contraindicated, and then CT with contrast is acceptable.

Subsequent scans:

All subsequent scans should be performed in the same manner (eg, with the same contrast, MRI field strength) as at screening preferably on the same scanner. If the imaging modality must be altered (eg, unscheduled assessment), consultation with the medical monitor is recommended.

Subsequent brain MRI/CT 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, will be performed independent of treatment cycle 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 **BICR**-confirmed disease **progression** per RECIST 1.1, **death, withdrawal of consent,** start of new anticancer therapy, or **end of study**, whichever occurs first. Any unscheduled scans should be submitted to the central imaging core laboratory.

Scans will be submitted to a central imaging core laboratory for archival, response assessment by BICR including RECIST 1.1, and/or [redacted]. Detailed information regarding submission of images to the central imaging core laboratory is found in the Site Imaging Manual.

**The site principal investigator will make final treatment and subject management decisions. Subjects who discontinue study treatment for reasons other than BICR-confirmed disease progression will continue to have tumor assessments (if clinically feasible) until disease progression is confirmed by BICR.**

### 8.3.2 Blinded Independent Central Review (BICR)

All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor for BICR. In addition, images (including Imaging Manual-defined acceptable modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but captures radiologic progression based on investigator assessment should also be submitted to the central imaging vendor.

When the investigator identifies radiographic progression per RECIST 1.1, the current imaging and all images to date must be immediately sent to the central imaging vendor. An expedited review of progression will be performed by central vendor, as detailed in the Site Imaging Manual, to inform real-time patient treatment decisions.

**Treatment** will continue until BICR-**confirmed** disease progression per RECIST 1.1, death, withdrawal of consent, start of new anticancer therapy, or end of study, whichever occurs first.

The site principal investigator will make final treatment and subject management decisions **(refer to Section 6.1.7)**. **Subjects who discontinue study treatment for reasons other than BICR-confirmed disease progression will continue to have tumor assessments (if clinically feasible) until disease progression is confirmed by BICR.**

Following **documented** radiographic progression, the subject may remain on study treatment **provided criteria are met**. Refer to Section 6.1.7. **Any subsequent (investigator determined) progressive disease per RECIST 1.1 from a new baseline set at initial progression will result in permanent discontinuation of study treatment**.

## 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

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 CRF. 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 CRF. Record all measurements on the vital signs CRF.

**Table 8-1. Vital Signs for Subjects Receiving Tarlatamab**

| **Cycle 1** | |
|---|---|
| Day 1 and Day 8 | • Pre-infusion ± 5 minutes<br>• EOI ± 5 minutes<br>• 1 hour post-EOI ± 10 minutes |
| For subjects that require monitoring for restarting due to delays between doses (refer to Table 6-3); collect vital signs according to the timepoints in cycle 1 day 1 and day 8 guidance. Vital signs thereafter will be collected as indicated in the Schedule of assessments (see Section 1.3), including scheduled visits on cycle 1 day 2 and cycle 1 day 9. | |

EOI = end of infusion

### 8.4.2 Electrocardiograms

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

**Single ECGs**

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: heart rate, QRS, QT, QTc, and P-R 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. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary and legally permissible. 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 Activities (see Section 1.3). Echocardiogram/MUGA should include an evaluation from left ventricular ejection fraction. Additional ECHO/MUGA assessments may be performed as clinically indicated.

#### 8.4.5.2 Cytokine Release Syndrome

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 study, 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 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 HBV surface antigen [HBsAg-negative] and presence of HBV core antibody [anti-HBc positive]; and subjects with chronic HBV infection inactive carrier state, defined as presence of HBV surface antigen [HBsAg-positive] 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 SFU.

Subjects with chronic HBV infection inactive carrier state should be evaluated 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 anticancer therapies, however, they should also be potentially

evaluated for HBV prophylaxis as per an HBV specialist following local or institutional guidelines.

Any subject in which HBV DNA viral load becomes 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 positivity and no clinical signs of hepatitis do not require HBV DNA monitoring.

#### 8.4.5.5 Hypersensitivity

Hypersensitivity reactions have been reported in subjects treated with tarlatamab including rare severe events. Clinical signs and symptoms of hypersensitivity may include but are not limited to rash and bronchospasm. Monitor subjects 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.

#### 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, 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. Tumor lysis syndrome will be graded based on CTCAE v5.0 but will be managed based on Cairo Bishop criteria (Coiffier et al, 2008).

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product(s) or noninvestigational product(s)/auxiliary medicinal product(s) through the

SFU visit **or 60 days after the last dose of the study treatment, whichever is later,** are reported using the Events CRF.

Disease progression is an efficacy endpoint. Disease progression of SCLC is not considered an adverse event and should not be reported as an adverse event **unless there is evidence as suggesting a causal relationship between the investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and progression or symptom/sign of progression of the SCLC** as indicated in Section 11.4. Progression of the subject's underlying malignancy will be recorded in the Tumor Response CRF page as part of efficacy data collection and not on 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 study treatment, whichever is later,** are recorded in the subject's medical record and are submitted to Amgen or its designee using the Events CRF.

Disease progression and death due to disease progression of SCLC are not considered serious adverse events and will not be reported as serious adverse event **unless there is evidence as suggesting a causal relationship between the investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and progression or symptom/sign of progression of the SCLC** as indicated in Section 11.4. Progression of the subject's underlying malignancy will be recorded in the Tumor Response CRF page as part of efficacy data collection and not on the Events CRF. Death due to disease progression is to be recorded in the End of Study CRF page and not on the Events CRF.

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

Since the criteria of the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of

life-threatening status), it will be left to the investigator's judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.

#### 8.4.6.1.3 Serious Adverse Events After the Protocol-required Reporting Period

During the long-term follow-up period, if the investigator becomes aware of serious adverse event suspected to be related to tarlatamab 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 24 hours after the investigator's awareness of the event on the Events CRF.

Disease progression and death due to disease progression of SCLC are not considered serious adverse events and will not be reported as serious adverse events **unless there is evidence as suggesting a causal relationship between the investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and progression or symptom/sign of progression of the SCLC** as indicated in Section 11.4. Progression of the subject's underlying malignancy will be recorded in the Tumor Response CRF page as part of the efficacy data collection and not on the Events CRF. Death due to disease progression is to be recorded in the End of Study CRF and not 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 after 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. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire 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 after investigator's 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 noninvestigational product(s)/auxiliary medicinal product(s) because of a serious adverse event, this information must be submitted to Amgen.

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

The sponsor 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 external review body and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions **will be reported by the sponsor** according to local regulatory requirements **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 external review body, if appropriate according to local requirements.

For studies in which the treatment assignment is blinded, 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 in the European Union) for the Amgen Investigational Product. To ensure that consolidated safety information for the study is provided, this single DSUR will also include appropriate information on any other investigational products used in the clinical study, 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 paper-based electronic Serious Adverse Event (eSAE) Contingency Report Form.

Further details and definitions regarding OSF/SS - medication errors, misuse, and 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, if indicated, female partners of male subjects will be collected after the start of study treatment and until **60** days after last dose of investigational product/noninvestigational product(s)/auxiliary medicinal product(s).

If a pregnancy is reported, the investigator is to inform Amgen immediately and no later than 24 hours of learning of the pregnancy and/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 highly sensitive serum pregnancy test should be completed at screening and < 7 days **prior to initiation of investigational product** and serum or urine test completed on day 1 of each cycle, at **end of treatment**, and at SFU for females of childbearing potential (Section 1.3).

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

Additional pregnancy testing (serum or urine) should be performed on day 1 of each cycle, at end of treatment, at SFU and **60** days after last dose of tarlatamab (Section 1.3).

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

Blood samples will be collected for measurement of serum concentrations of tarlatamab as specified in the Schedule of Activities (Section 1.3). **Blood must not be drawn from a port catheter during investigational product infusion. 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. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of collection for each sample will be recorded. In case the PK sample is not collected within the scheduled window, it will not be considered a protocol deviation.**

## 8.6 Pharmacogenetic Assessments

There are no pharmacogenetic assessments in this study.

## 8.7 Antibody Testing Procedures

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

Refer to 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 Medical Resource Utilization and Health Economics

Medical resource utilization data, associated with medical encounters (including but not limited to CRS, ICANS, etc) 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 may 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-mandated procedures, tests, and encounters are excluded from the analysis of health resource utilization and health economics.

The data collected may be used to conduct exploratory 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

No statistical hypotheses will be tested.

## 9.2 Sample Size Determination

Approximately 30 subjects will be enrolled in the study. With 30 subjects enrolled at the target dose, the probability that the observed ORR will be greater than **different thresholds are presented in Table 9-1**.

**Table 9-1. Probabilities of Observed ORR Greater Than Thresholds With Sample Size of 30**

| True ORR | Probability of Observed ORR > 25 % | Probability of Observed ORR > 30% |
|---|---|---|
| **0.35** | **88%** | **64%** |
| **0.4** | **96%** | **82%** |

ORR = overall response rate

With 30 subjects, there is a 79% to 96% probability of observing at least 1 adverse event if the true event rate is 5% to 10%.

## 9.3 Populations for Analysis

The following populations are defined:

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

Note: Additional populations for efficacy analyses will be defined in the SAP.

### 9.3.1 Covariates

The relationship of covariates to efficacy endpoints will be explored if appropriate.

## 9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses.

### 9.4.1 Planned Analyses

#### 9.4.1.1 Primary Analysis

The primary analysis is planned **after** all subjects have been enrolled and have had opportunity to **confirm an objective response** after **the** first post-treatment scan **or up to 13 weeks of follow-up, whichever occurs first**.

The data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan. The data supporting the primary analysis

will be locked. It is expected that outstanding data issues are resolved ahead of the lock to the extent possible.

#### 9.4.1.2 Final Analysis

The final analysis will occur when enrollment is complete and each subject completes the study, including long-term follow-up.

The data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan. The data supporting the final analysis will be locked to prevent future changes. It is expected that all outstanding data issues are resolved ahead of the final lock.

### 9.4.2 Methods of Analyses

#### 9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, and PK. 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.

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

#### 9.4.2.2 Efficacy Analyses

| Endpoint/Estimand | Statistical Analysis Methods |
|---|---|
| **Primary** | |
| Objective Response Rate (ORR) | Summarized along with a Clopper-Pearson exact binomial CI. Subjects without a post-baseline tumor assessment will be considered non-responders. |
| Duration of Response (DOR) | Summarized with Kaplan-Meier estimate and 95% CI for quartiles and rates for select durations |
| Disease Control Rate (DCR) | Analyzed by the same methods used to analyze ORR. The summary of clinical benefit (ie, percentages of subjects with duration of disease control ≥ 4 months) will be provided. The percent change from baseline in target lesion sum of diameters will be plotted. |
| Progression-free survival (PFS) | Analyzed by the same methods used to analyze DOR |
| Overall Survival (OS) | Analyzed by the same methods used to analyze DOR |

#### 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 and coded using Medical Dictionary for Regulatory Activities (MedDRA). Tables of grade 3 or higher treatment-emergent adverse events, fatal treatment-emergent adverse events, serious treatment-emergent adverse events, treatment-emergent adverse events leading to discontinuation from investigational product and treatment-related adverse events will also be provided.

##### 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

Single ECGs

The single 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

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

#### 9.4.2.3.8 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term 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 or model-predicted Bayesian estimates will be utilized to drive the qualitative (graphical) and quantitative relationship of tarlatamab exposures with relevant efficacy or safety variables. The efficacy/safety variables will be aligned with primary and 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 |
|---|---|
| 1L | first-line |
| Ab | antibody |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BICR | blinded independent central review |
| BIL | bilirubin |
| BiTE | bispecific T-cell engager |
| BOR | overall response |
| C1D1 | cycle 1 day 1 |
| C1D8 | cycle 1 day 8 |
| C1D15 | cycle 1 day 15 |
| CFR | U.S. Code of Federal Regulations |
| CNS | central nervous system |
| CR | complete response |
| CRF | Case Report Form |
| CRS | cytokine release syndrome |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DC | disease control |
| DILI | drug-induced liver injury |
| DOR | duration of response |
| DLL3 | Delta-like ligand 3 |
| DMC | data monitoring committee |
| DRT | data review team |
| DSUR | Development Safety Update Report |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| ED | extensive disease |
| EDC | electronic data capture |
| eSAE | electronic Serious Adverse Event |
| **FDA** | **Food and Drug Administration** |
| FDG-PET | fluorodeoxyglucose-positron emission tomography |
| FSH | follicle-stimulating hormone |

| | |
|---|---|
| GCP | Good Clinical Practice |
| HLE | extended half-life |
| HBV | hepatitis B virus |
| HBsAg | hepatitis B virus surface antigen |
| HCV | hepatitis C virus |
| ICE | Immune-effector cell-associated encephalopathy |
| ICF | informed consent form |
| ICANS | Immune effector cell-associated neurotoxicity syndrome |
| ICH | International Council for Harmonisation |
| INR | international normalized ratio |
| IRT | interactive response technology |
| IV | intravenous |
| LTFU | long-term follow-up |
| MRI | magnetic resonance imaging |
| NCT | National Clinical Trials |
| NE | not evaluable |
| NSCLC | non-small cell lung cancer |
| ORR | objective response rate |
| OS | overall survival |
| OSF | other safety finding |
| PCR | polymerase chain reaction |
| PD | progressive disease |
| PD-1 | Programmed Cell Death Protein 1 |
| PD-(L)1 | Programmed Cell Death Ligand 1 |
| PET-CT | positron emission tomography–computed tomography |
| PFS | progression-free survival |
| PK | pharmacokinetic |
| PR | partial response |
| QTc | corrected QT interval |
| QTL | quality tolerance limit |
| RECIST 1.1 | Response Evaluation Criteria in Solid Tumors Version 1.1 |
| scFc | single-chain fragment crystallizable |
| SCLC | small cell lung cancer |
| 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 |

## 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).

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

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

**Table 11-1. Analyte Listing**

| Local Laboratory: Chemistry | Local Laboratory: Coagulation | Local Laboratory: Urinalysis | Local Laboratory: Hematology | Other Lab Analytes |
|---|---|---|---|---|
| Sodium<br>Potassium<br>Chloride<br>Bicarbonate or $CO_2$<br>Total protein<br>Albumin<br>Calcium<br>Magnesium<br>Phosphorus<br>Glucose<br>BUN or serum urea<br>Creatinine<br>Creatine Kinase<br>Uric acid<br>Total bilirubin<br>Direct bilirubin<br>ALP<br>LDH<br>AST (SGOT)<br>ALT (SGPT) | PT/INR<br>PTT/APTT | Blood<br>Protein<br>Glucose<br>Bilirubin | RBC<br>Hemoglobin<br>MCV<br><br>Platelets<br>WBC<br>Differentials:<br>5-part differential:<br>• Lymphocytes<br>• Monocytes<br>• Eosinophils<br>• Basophils<br>• Total Neutrophils or (Segmented Neutrophils and bands/stabs<br>*3-part differential if unable to perform 5-part:*<br>• Lymphocytes<br>• Granulocytes<br>• Monocytes<br>OR<br>• Lymphocytes<br>• Neutrophils<br>• Mid-cell fraction | <u>Central Laboratory</u>:<br>Anti-tarlatamab antibodies<br>Tarlatamab PK<br><br><u>Local Laboratory</u>:<br>Serum or Urine Pregnancy<br>HIV Antibody testing<br>Hepatitis serology testing (DNA/RNA by PCR as needed)<br>Hep B surface antigen<br>Hep B core antibody<br>Hep C virus antibody<br>Amylase<br>Lipase<br>TSH<br>FT4 |

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; APTT = activated partial thromboplastin time; BUN = blood urea nitrogen; $CO_2$ = carbon dioxide; DNA = deoxyribonucleic acid; FT4 = free T4 Hep = hepatitis; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; PCR = polymerase chain reaction; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid-stimulating hormone; WBC = white blood cell count

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

**Table 11-2. DILI Potential Analyte Listing**

| | |
|---|---|
| Chemistry | Total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin |
| Hematology | Hemoglobin, Platelets, RBC Morphology, 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, Immunoglobulin G, Liver Kidney AB 1,<br>Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody |
| Toxicology | Acetaminophen |

AB = antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; APTT = activated partial thromboplastin time; DILI = drug-induced liver injury; EDA = early antigen; Ig = immunoglobulin; 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

### 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 external review body (eg, institutional review board [IRB]/Independent ethics committee [IEC]/regulatory authorities) by the investigator and reviewed and approved by the external review body. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the external review body 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, if applicable, from the external review body and amended protocol investigator's Signature page to Amgen before 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 external review body, as appropriate.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the external review body annually or more frequently in accordance with the requirements, policies, and procedures established by the external review body.
- Obtaining, if applicable, annual external review body approval/renewal throughout the duration of the study. Copies of the investigator's reports and the external review body continuance of approval must be sent to Amgen.
- Notifying the external review body of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures.

- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the external review body, and all other applicable local regulations.

**Informed Consent Process**

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

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

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

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The person who conducted the informed consent discussion (investigator or their delegated representative) must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have their primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, (or it is a local requirement) 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 their notification of the primary care physician is to be documented in the subject's medical

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

If a potential subject is illiterate or visually impaired and does not have a legally 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.

**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 informed consent forms) are to be kept in confidence by the investigator, except as described below.

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

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

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

Amgen complies with all relevant and applicable laws and regulations that protect personal information 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.

**Serious Breach**

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

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

- Good Clinical Practice (GCP)
- the clinical trial protocol
- an applicable regulation

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

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

**Publication Policy**

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

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.

**Results Reporting**

Results will be reported to clinical study registries in accordance with applicable regulatory requirements. The final summary results will be reported after the global end of study (as defined in Section 4.5) to ensure data from all sites globally are included in the reported results.

**Investigator Signatory Obligations**

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

The coordinating investigator, identified by Amgen, will be any or all 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, external review body review, 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 parameters (QTLs) 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 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 in the Interactive Response Technology system (if used, such as subject ID 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, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation, and all correspondence to and from the external review body and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Noninvestigational 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.

**Study and Site Closure**

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

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) by 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.<br>• 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.<br>• Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan. |
| **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).<br>• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected intentional overdose of either study treatment or a concomitant medication.<br>• Intentional overdose will be reported as an adverse event/serious adverse event when it is taken with possible suicidal/self-harming intent. Such intentional overdoses are to be reported regardless of sequelae on the Events CRF.<br>• Accidental/unintentional overdose will be captured as a medication error.<br>• Disease progression is an efficacy endpoint. Progression or symptom/sign of the small cell lung cancer (SCLC) should ONLY be reported as an adverse event or serious adverse event if there is evidence suggesting a causal relationship between the investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) and progression or symptom/sign of progression of the SCLC. The event should be **recorded** on the Events CRF.<br>• “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. |
| **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.
- Progression of the SCLC should be considered disease progression and not considered an adverse event or serious adverse event. Progression of the subject's underlying malignancy will be recorded in the Tumor Response CRF as part of efficacy data collection and not on the Events CRF. Death due to disease progression is to be recorded on the End of Study CRF page and not on the Events form.

  The following are not considered adverse events or serious adverse events:

  - Progression of SCLC (Progressive disease): If progressive disease is consistent with progression of the underlying malignancy as defined by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) (See Section 11.10)
  - Clinical symptoms or signs that meet the expected pattern of disease progression of the SCLC in the presence of documented evidence of progression underlying malignancy as defined by RECIST 1.1 (See Section 11.10)
  - Deaths that are attributed by the investigator to progression of SCLC

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

**Other Safety Findings/Special Situations: Medication Errors, Misuse or Abuse**

All medication errors, misuse or abuse **of the investigational product** when associated with a serious adverse event**, the OSF/SS** must be reported to Amgen or designee immediately and no later than 24 hours of investigator's awareness by submitting the paper-based electronic Serious Adverse Event (eSAE) Contingency Report Form.

| | |
|---|---|
| Definitions | Medication Error: A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the participant (eg, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice. |
| | Misuse: A misuse refers to situations where the medicinal product, combination product, or medical device is intentionally and inappropriately used not in accordance or outside what is foreseen in the protocol. |
| | Abuse: An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, combination product, or medical device, which is accompanied by harmful physical or psychological effects. |

**Recording Adverse Events and Serious Adverse Events**

| **Adverse Event and Serious Adverse Event Recording** |
|---|
| • When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.<br>• The investigator will then record all relevant adverse event/serious adverse event information in the Events CRF.<br>• The investigator must assign the following mandatory adverse event attributes:<br>– Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)<br>– Dates of onset and resolution (if resolved)<br>– Did the event start before first dose of investigational product<br>– Assessment of seriousness<br>– Severity (or toxicity defined below)<br>– Assessment of relatedness to investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s)<br>– Assessment of relatedness to study-required activity and/or procedures is only required for Serious Adverse Events<br>– Action taken<br>– Outcome of event<br>• 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.<br>• 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, except for the subject number, will be blinded on the copies of the medical records before submission to Amgen.<br>• 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 assess severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:<br>The Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 which is available at the following location:<br>http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. |

CTCAE will be used with the following exceptions: Cytokine release syndrome (CRS) and immune-effector cell associated neurologic syndrome (ICANS) will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) (Lee et al, 2019) as described in Section 11.11. Tumor lysis syndrome (TLS) will be graded based on CTCAE v5.0 but will be managed based on Cairo Bishop criteria (Coiffier et al, 2008).

**Assessment of Causality**

- The investigator is obligated to assess the relationship between investigational product(s) investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), and each occurrence of each adverse event.
- The investigator is obligated to assess the relationship between investigational product(s) investigational product(s), noninvestigational product(s)/auxiliary medicinal product(s), study-required activity and/or procedure(s) and each occurrence of each serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the investigator's brochure and/or product information, for marketed products, in their 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 assess causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change their opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. In this case, for sites reporting serious adverse events via EDC, the investigator or sub-investigator must reconfirm causality in the EDC system within 72 hours of the serious adverse event being entered on the Events CRF.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

**Follow-up of Adverse Event and Serious Adverse Event**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare 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 eSAE Contingency Report Form) (see Figure 11-1) immediately and no later than 24 hours of the investigator's awareness of the event.
- If the event is a serious adverse event associated with the Other Safety Finding/Special Situation (medication error, misuse or abuse) then the site must complete/submit the paper-based eSAE Contingency Report Form (see Figure 11-1) for the associated Other Safety Finding/Special Situation (medication error, misuse or abuse) and this is the primary reporting method.
- 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 (see Figure 11-1) to report the event.

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

AMGEN
Study # 20230273
AMG 757

**Clinical Trial Electronic Serious Adverse Event Contingency Report Form**

For Restricted Use

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

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

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

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

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

***AGS Inbound - CN svc-ags-in-cn@amgen.com***

***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<br>If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report<br>OR<br>Other Safety Finding/Special Situation associated with a Serious Adverse Event<br>*List one event per line.* | Date Started<br>Day Month Year | Date Ended<br>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 (AMG757)> No | < Tarlatamab (AMG757)> Yes | <Device> No | <Device> Yes | <Device> No | <Device> Yes | <Device> No | <Device> 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<br>Day Month Year | Date Discharged<br>Day Month Year |
|---|---|
| | |

## 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 OR for pediatric studies: who have reached puberty 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 **an additional 60** days after the last dose of tarlatamab. **Note: contraception requirements for noninvestigational medicinal product(s)/auxiliary medicinal product(s) including auxiliary medicinal products are based on regional/local prescribing information.**

**Definition of Females of Childbearing Potential**

A female is considered fertile after 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.
- 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 (if 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 study 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 noninvestigational product(s)/auxiliary medicinal product(s); the reliability of sexual abstinence must be evaluated in relation to the duration of the study 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 noninvestigational medicinal product(s)/auxiliary medicinal product(s) including auxiliary medicinal products are based on regional/local 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 nonchildbearing potential or has had a bilateral tubal ligation/occlusion or if the male has had a vasectomy and testing confirms there is no sperm in the semen, 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.
- 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 noninvestigational 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.
- 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 tarlatamab through **60** days after the last dose of tarlatamab.

## Figure 11-2. Pregnancy and Lactation Notification Forms (Paper-based Form)

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: 20230273

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:** 20230273

**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, 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 before being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

When permitted by local regulations and if informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the SCLC, the dose response and/or prediction of response to tarlatamab, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 5 years after the study is finished.

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

The subject retains the right to request that the sample material be destroyed by contacting the investigator. After 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 and according to the approval of local laws and regulations. However, information collected from samples before the request for destruction, will be retained by Amgen.

All rights in inventions and discoveries that are made or developed by Institution, Investigator and/or Study Personnel as a result of the conduct of the Study, other than Registrational Research Inventions, ("Exploratory Research Inventions") shall be owned by both Institution and Sponsor equally.

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

Subjects with abnormal hepatic laboratory values **such as** alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), alkaline phosphatase [ALP], 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)**. **This instruction is based on the FDA** Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (**US FDA,** July 2009).

**Reporting and management of hepatotoxicity in subjects in clinical trials is described below and management is summarized in the flow chart in Figure 11-3.**

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

**S**topping 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 upper limit of normal (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 of 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 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 **protocol-required therapies** 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 **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 **study drug**(s) has/have been discontinued AND the subject is asymptomatic.

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

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

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

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

#### 11.7.3.1 Investigating Alternative Causes of Hepatotoxicity

- The following **assessments** are to be considered depending on the clinical situation:
- **B**lood count with differential to assess for eosinophilia.
- Serum total immunoglobulin G, anti**-**nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis.
- Serum acetaminophen (paracetamol) levels.
- A more detailed history of:
    - **p**rior and/or concurrent diseases or illness
    - **e**xposure to environmental and/or industrial chemical agents
    - **s**ymptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever

- **p**rior and/or concurrent use of alcohol, recreational drugs, and special diets
- **c**oncomitant use of medications (including non**-**prescription medicines and herbal and dietary supplements), plants, and mushrooms

- Viral serologies.
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear.
- Appropriate liver imaging if clinically indicated.
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected.
- Hepatology consult (**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, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
- exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms.
- heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- alpha-one antitrypsin deficiency
- alcoholic hepatitis
- autoimmune hepatitis
- Wilson's disease and hemochromatosis
- NASH (nonalcoholic fatty liver disease aka 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. 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 subjects is required, and continuation of the medication may be considered and will be at the discretion of the investigators.**

### 11.7.4 Rechallenge and Dose Modification in Patients with Suspected Hepatotoxicity in Oncology Trials

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

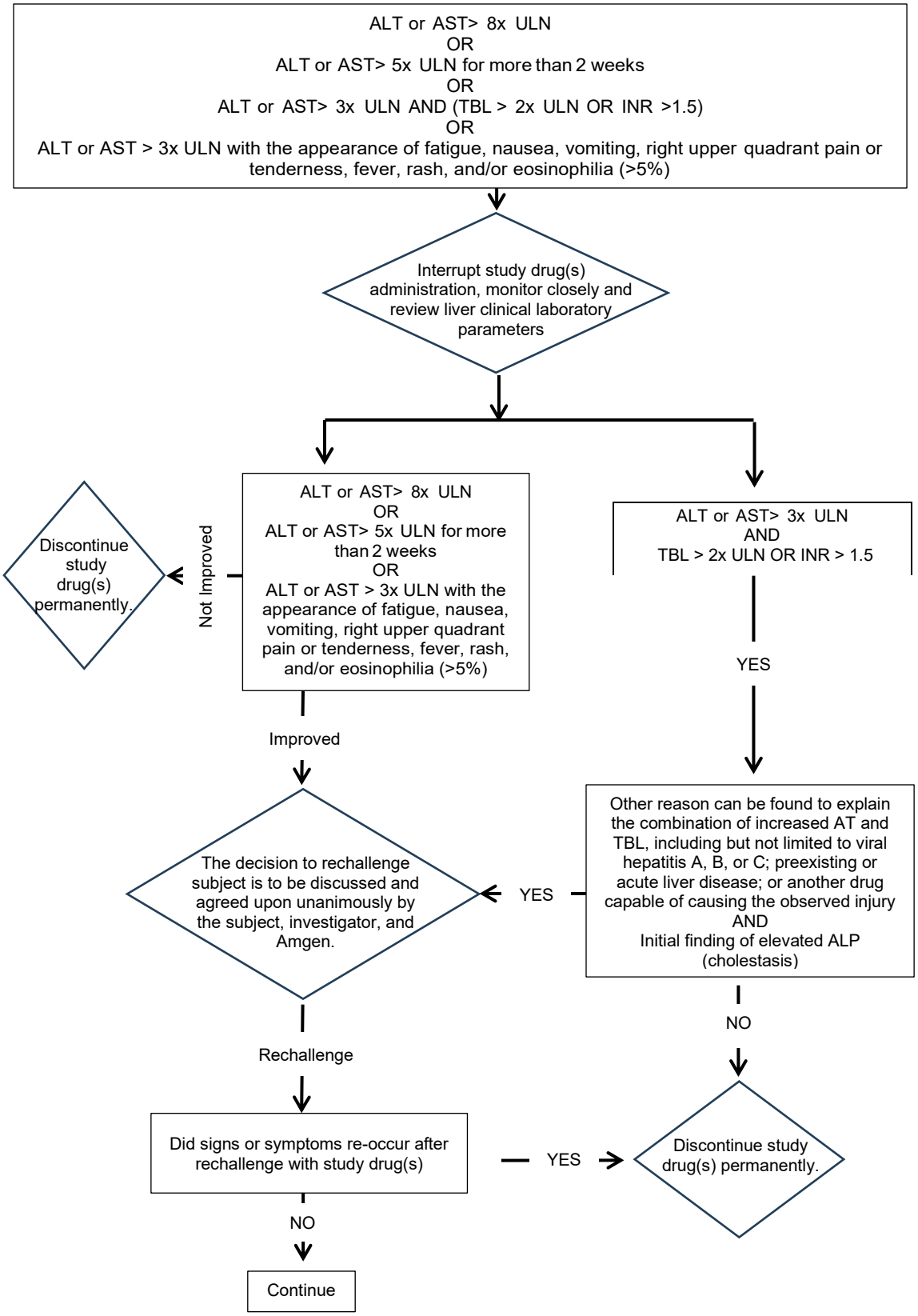
### 11.7.5 Permanent Discontinuation of Study Drug(s)

**In the absence of acceptable enzyme level decrease or lack of a plausible alternative explanation for the elevated 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 (Figure 11-3).**

**Figure 11-3. Management of Potential Hepatotoxicity**



## 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 United States Food and Drug Administration (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 Appendix 11.4.

**Anticipated Serious Adverse Events for Study 20230273**

| MedDRA Preferred Term[a] |
|---|
| cough |
| weight loss |
| decreased appetite |
| anorexia |
| hemoptysis |
| small cell lung cancer |
| metastasis |
| chest pain |
| fatigue |
| anemia |

MedDRA = Medical Dictionary for Regulatory Activities
[a] MedDRA Version 24.0

## 11.9 Appendix 9. ECOG Performance Status and NYHA Functional Classification

Eastern Cooperative Oncology Group (ECOG) Performance Status

- 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 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 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 one 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.

[redacted]

#### 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 one 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 CRF (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 one 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. |

PR = partial response; SD = stable disease

[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 SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

### 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 first dose of tarlatamab 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 | (Non-CR/Non-PD)[a] |
| NA | CR or Non-CR/Non-PD | NE | (Non-CR/Non-PD)[a] |
| NA | PD | Any | PD |
| NA | Any | Yes | PD |
| NA | NE | No | NE |

CR = complete response; NA = Not applicable; NE = Not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Per RECIST 1.1, “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 When Confirmation of Complete Response (CR) and Partial Response (PR) Required**

| Overall Response First Time Point | Overall Response Second Time Point | Best Overall Response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[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 one 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 partial response (PR) or SD and one 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 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.

### 11.11.2 Specific Guidance for Immune-effector Cell-associated Neurologic Syndrome

For this trial, immune-effector cell associated neurologic syndrome (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**

- 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 two 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 to 9, grade 1
- 3 to 6, grade 2
- 0 to 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 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.<br>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 hemorrhage 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)

- Neurologic assessment and grading at least twice a day to include cognitive assessment and motor weakness

- MRI of the brain with and without contrast (or brain CT if MRI is not feasible) for ≥ grade 2 neurotoxicity
- Neurology consultation at first sign of neurotoxicity
- Conduct electroencephalogram (EEG) for seizure activity for ≥ grade 2 neurotoxicity
- Aspiration precautions; IV hydration
- Use caution when prescribing medications that can cause central nervous system (CNS) depression (aside from those needed for seizure prophylaxis/treatment)

### 11.11.3 Tumor Lysis Syndrome

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 classifies 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 11-8) 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 11-8).

**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 20230273 2

**Document Description:** Tarlatamab 20230273 PA1- development for a China only study

**Document Number:** CLIN-000332994

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**Type of Study Protocol:** Amendment

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| Document Approvals | |
|---|---|
| Reason for Signing: Management | Name: [redacted]<br>Date of Signature: 06-Sep-2024 15:25:09 GMT+0000 |

**Amendment 1**

**Protocol Title: Phase 2a Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of Tarlatamab in Chinese Subjects with Advanced Small Cell Lung Cancer after Two or More Prior Lines of Treatment (DeLLphi-307)**

Amgen Protocol Number: 20230273

Amendment Date: 15 May 2024

**Rationale:**

This protocol is mainly being amended to update the objectives and endpoints to include efficacy as a primary endpoint and pharmacokinetics (PK) as secondary endpoint along with safety and tolerability. Changes including, but not limited to, the following were incorporated into the protocol:

- Updated the phase throughout the protocol from a phase 1b to a phase 2a.
- Updated the protocol to replace mention of “preliminary anti-tumor activity” to “efficacy” throughout the protocol.
- Updated the objectives and endpoint sections to:
  - clarify that the primary objective was to evaluate efficacy of tarlatamab as assessed by objective response rate (ORR) based on blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1).
  - Incorporate two new efficacy secondary endpoints to:
    - evaluate the efficacy of Tarlatamab as assessed by ORR based on investigator assessment per RECIST 1.1.
    - evaluate efficacy of Tarlatamab as assessed by duration of response (DOR), disease control (DC), and progression-free survival (PFS), based on BICR and investigator assessment per RECIST 1.1.
    - evaluate efficacy of Tarlatamab as assessed by overall survival (OS)

  - include PK and immunogenicity as secondary endpoints
  - include estimand(s) for primary objective(s)

- Updated overall design section to clarify that Chinese subjects will include those with advanced small cell lung cancer (SCLC) who have progressed on or recurred following 1 platinum-based regimen as 1L therapy (including a PD-1/PD-[L]1) and at least 1 other prior line of therapy (re treatment with a platinum-based regimen is considered a second-line of therapy).
- Updated the number of Chinese subjects in this study from 15 to 30.
- Monitoring guidance for subjects has been updated from a minimum of 24 hours post-infusion to 6 to 8 hours for cycle 1 day 1 and cycle 1 day 8 throughout the protocol where applicable.
- Added a new section (Section 4.4) to capture details on the justification for monitoring.
- Updated Table 8-1 (Section 8.4.1) to align with Schedule of Activities (Section 1.3).
- Updated radiological imaging assessment section (Section 8.3.1) to clarify that scans will be submitted to a central imaging core laboratory for archival, response assessment by BICR including RECIST 1.1, and/or [redacted].
- Incorporated new BICR Section (Section 8.3.2).
- Updated antibody testing procedure (Section 8.7) to clarify that samples testing positive for binding antibodies will be evaluated for anti-tarlatamab neutralizing antibodies.
- Updated statistical consideration section (Section 9) to update the sample size determination, planned analyses, population for analysis, and exposure to investigational product language.
- Updated Appendix 3 (Section 11.3) to incorporate quality tolerance limit parameters (QTLs) language.

- General editorial changes, including administrative, abbreviations, typographical, and formatting corrections have been made throughout the protocol for clarification.

**Amendment 2**

# Phase 2a Study Evaluating the Efficacy, Safety, Tolerability and Pharmacokinetics of Tarlatamab in Chinese Subjects with Advanced Small Cell Lung Cancer after Two or More Prior Lines of Treatment (DeLLphi-307)

Amgen Protocol Number AMG 757 20230273

NCT Number: NCT06502977

Amendment Date: 06 September 2024

**Rationale:**

This protocol has been amended to align with the United States Prescribing information for tarlatamab and other clarifications throughout the protocol. Changes including the following were incorporated into the protocol:

- Addition of the NCT number
- Addition of language regarding the accelerated approval of tarlatamab from the United States Food and Drug Administration
- Revision of the duration of the safety follow-up visit for alignment with the tarlatamab approved label
- Revision of disease progression language to specify that subjects will receive study treatment until blinded independent central review-confirmed disease progression per RECIST 1.1, death, withdrawal of consent, start of new anticancer therapy, unacceptable toxicity, or end of study as determined by the sponsor (whichever occurs first)
- Clarification of the New York Heart Association data collection
- Clarification of the timing of screening local laboratory assessments
- Clarification of the timing of laboratory assessments prior to cycle 1 day 1 dose
- Revision of inclusion criterion to clarify that extensive-stage small cell lung cancer could be enrolled
- Revision of contraception and lactation language to align the timing with the tarlatamab approved label
- Addition of dose modification guidance for hypersensitivity (allergic reactions)
- Safety language was updated when applicable to align with most recent guidance from Amgen safety and pharmacovigilance.
- Hepatoxicity guidelines were updated to align with most recent guidance from Amgen safety
- Addition of End of Treatment section