CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761344Orig1s001

Trade Name:	IMDELLTRA
Generic or Proper Name:	tarlatamab-dlle
Sponsor:	Amgen Inc.
Approval Date:	November 19, 2025
Indication:	IMDELLTRA is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T-cell engager indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

BLA 761344/S-001

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING
REQUIREMENTS

Amgen Inc.
Attention: Michelle Garcia
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Michelle Garcia:

Please refer to your supplemental biologics license application (sBLA) received June 18, 2025, and your amendments, submitted under section 351(a) of the Public Health Service Act for Imdelltra (tarlatamab-dlle) injection.

This Prior Approval sBLA provides for conversion from accelerated approval to traditional approval of Imdelltra (tarlatamab-dlle) for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy, in addition to fulfillment of Postmarketing Requirements 4635-1 and 4635-2.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on June 18, 2025, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761344/S-001**." Approval of this submission by FDA is not required before the labeling is used.

SUBPART E FULFILLED

We approved this BLA under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 601.41.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submission dated June 18, 2025, containing the final report for the following postmarketing requirements listed in the May 16, 2024, approval letter for BLA 761344.

4635-1 Conduct a multicenter randomized clinical trial intended to verify and describe the clinical benefit of tarlatamab in patients with extensive stage small cell lung cancer (ES-SCLC) who have had disease progression on or after platinum-based chemotherapy.

4635-2 Conduct an integrated safety analysis of data from patients with extensive stage small cell lung cancer to further characterize the long-term incidence, severity, and outcome of the known serious risks of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and neurologic toxicity. Include a comprehensive analysis from all available data sources including but not limited to patient-level and pooled analyses of ongoing and completed clinical trials. These data could also be obtained from the confirmatory trial titled “A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared with Standard of Care in Subjects with Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy (DeLLphi-304)”.

We have reviewed your submission and conclude that the above requirements were fulfilled.

We remind you that there are postmarketing commitments listed in the May 16, 2024, approval letter that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

601.12(f)(4)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety-related information [21 CFR 601.12(f)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(f)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Ashley Lane, Senior Regulatory Health Project Manager, at Ashley.Lane@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Erin Larkins, M.D.
Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information
  - Medication Guide

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIN A LARKINS
11/19/2025 01:01:36 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761344Orig1s001

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IMDELLTRA® safely and effectively. See full prescribing information for IMDELLTRA.

IMDELLTRA® (tarlatamab-dlle) for injection, for intravenous use
Initial U.S. Approval: 2024

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME
See full prescribing information for complete boxed warning.

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving IMDELLTRA. Initiate treatment with the IMDELLTRA using step-up dosing schedule to reduce the incidence and severity of CRS. Withhold IMDELLTRA until CRS resolves or permanently discontinue based on severity. (2.5, 5.1)

Neurologic toxicity and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), including life-threatening or fatal reactions, can occur in patients receiving IMDELLTRA. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment and treat promptly. Withhold IMDELLTRA until ICANS resolves or permanently discontinue based on severity. (2.5, 5.2)

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	11/2025
Dosage and Administration (2.1, 2.2, 2.3)	11/2025
Dosage and Administration (2.4, 2.5, 2.6)	11/2025
Warnings and Precautions (5.1, 5.2, 5.3, 5.4)	11/2025
Warnings and Precautions, (5.5,5.6,5.7)	11/2025

----------INDICATIONS AND USAGE----------
IMDELLTRA is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T-cell engager indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy. (1)

----------DOSAGE AND ADMINISTRATION----------
Administer as an intravenous infusion over 1 hour. (2.2)
- Administer IMDELLTRA according to the step-up dosing schedule in Table 1 to reduce the risk of cytokine release syndrome. (2.2)
- Administer concomitant medications as recommended. (2.3)
- Monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting.
- Recommend patients to remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from the start of the infusion with IMDELLTRA following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver. (2.2)
- See Full Prescribing Information for instructions on preparation and administration. (2.2, 2.6)

----------DOSAGE FORMS AND STRENGTHS----------
- For injection: 1 mg of lyophilized powder in a single-dose vial for reconstitution and further dilution. (3)
- For injection: 10 mg of lyophilized powder in a single-dose vial for reconstitution and further dilution. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Cytopenias: Monitor complete blood counts prior to administration of all doses of IMDELLTRA up through Cycle 5 Day 15 and then prior to administration of IMDELLTRA on Day 1 of each cycle starting with Cycle 6. More frequent evaluation may be necessary as clinically indicated. Withhold or permanently discontinue based on severity. (5.3)
- Infections: Monitor for signs and symptoms of infection; treat appropriately. Withhold or permanently discontinue based on severity. (5.4)
- Hepatotoxicity: Monitor liver enzymes and bilirubin prior to administration of all doses of IMDELLTRA up through Cycle 5 Day 15 and then prior to administration of IMDELLTRA on Day 1 of each cycle starting with Cycle 6. More frequent evaluation may be necessary as clinically indicated. Withhold or permanently discontinue based on severity. (5.5)
- Hypersensitivity: Monitor for signs and symptoms of hypersensitivity and treat accordingly. Withhold or permanently discontinue based on severity. (5.6)
  Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception (5.7, 8.1, 8.3)

----------ADVERSE REACTIONS----------
- The most common adverse reactions (> 20%) were cytokine release syndrome, fatigue, decreased appetite, anemia, dysgeusia, pyrexia, constipation, musculoskeletal pain, and nausea.
- The most common (≥ 5%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased sodium, decreased total neutrophils, and increased uric acid.

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving IMDELLTRA. Initiate IMDELLTRA using the step-up dosing schedule to reduce the incidence and severity of CRS. Withhold IMDELLTRA until CRS resolves or permanently discontinue based on severity *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)]*.

Neurologic toxicity and immune effector cell-associated neurotoxicity syndrome (ICANS), including life-threatening or fatal reactions, can occur in patients receiving IMDELLTRA. Monitor patients for signs and symptoms of neurologic toxicity, including ICANS, during treatment and treat promptly. Withhold IMDELLTRA until ICANS resolves or permanently discontinue based on severity *[see Dosage and Administration (2.5) and Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

IMDELLTRA is indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- Administer IMDELLTRA according to the step-up dose and schedule in Table 1 to reduce the incidence and severity of cytokine release syndrome (CRS) *[see Dosage and Administration (2.2)]*.
- Evaluate complete blood count, liver enzymes and bilirubin prior to administration of all doses of IMDELLTRA up through Cycle 5 Day 15 and then prior to administration of IMDELLTRA on Day 1 of each cycle starting with Cycle 6. More frequent evaluation may be necessary if clinically indicated *[see Warnings and Precautions (5.3, 5.5)]*.
- Ensure patients are well hydrated prior to administration of IMDELLTRA *[see Warnings and Precautions (5.1)]*.
- For Cycle 1, administer recommended concomitant medications in Table 3 before and after Cycle 1 Day 1 and Cycle 1 Day 8 IMDELLTRA infusions to reduce the risk of CRS reactions *[see Dosage and Administration (2.3)]*.
- IMDELLTRA should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions, such as CRS and

neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS) *[see Warnings and Precautions (5.1, 5.2)]*.

- Due to the risk of CRS and neurologic toxicity, including ICANS, monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1, 5.2)]*.
- Recommend patients to remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver.
- Inform both the patient and the caregiver on the signs and symptoms of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) prior to discharge.

2.2 Recommended Dosage and Administration

- Administer IMDELLTRA as an intravenous infusion for one hour.
- The recommended step-up dose and schedule for IMDELLTRA is provided in Table 1. Administer step-up dose and schedule on Cycle 1 Day 1 to reduce the incidence and severity of CRS.
- After step-up dose and schedule on Cycle 1 Day 1, administer IMDELLTRA every 2 weeks until disease progression or unacceptable toxicity.

Table 1. Recommended Dose and Schedule of IMDELLTRA

Dosing Schedule	Day	Dose of IMDELLTRA	Administration Instructions	Recommended Monitoring
Step-up Dose and Schedule Cycle 1	Day 1[a]	Step-up dose[a] 1 mg	Administer IMDELLTRA as a 1-hour intravenous infusion in an appropriate healthcare setting.	Monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 in an appropriate healthcare setting. Recommend that patients remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from start of the IMDELLTRA infusion accompanied by a caregiver.
	Day 8[a]	10 mg[a]		

Dosing Schedule	Day	Dose of IMDELLTRA	Administration Instructions	Recommended Monitoring
	Day 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion[b]
Cycle 2	Day 1 and 15	10 mg		Observe patients for 6-8 hours post IMDELLTRA infusion[b].
Cycles 3 and 4	Day 1 and 15	10 mg		Observe patients for 3-4 hours post IMDELLTRA infusion[b].
Cycle 5 and subsequent infusions	Day 1 and 15	10 mg		Observe patients for 2 hours post IMDELLTRA infusion[b].

a. Administer recommended concomitant medications before and after Cycle 1 Day 1 and Cycle 1 Day 8 IMDELLTRA infusions as described in Table 3.

b. Extended monitoring in a healthcare setting is not required unless the patient experiences Grade ≥ 2 CRS, ICANS or neurological toxicity during prior treatments. See Tables 5 and 6 for monitoring recommendations.

Note: See Table 4 for recommendation on restarting IMDELLTRA after dose delays.

Administration

- The intravenous (IV) catheter for concomitant medications administration can be used to administer the IMDELLTRA infusion.
- To ensure patency, flush the IV catheter over 3 to 5 minutes using 0.9% Sodium Chloride for Injection.
- Administer the reconstituted and diluted IMDELLTRA as a 1-hour intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm. Flush the IV-line upon completion of the IMDELLTRA infusion.

Table 2 provides the infusion duration and rate.

Table 2. IMDELLTRA Infusion Duration and Rate

Infusion Duration for 250 mL IV Preparation	Infusion Rate
1 hour	250 mL/hour

2.3 Recommended Concomitant Medications for IMDELLTRA Administration for Cycle 1 Day 1 and Cycle 1 Day 8

Administer recommended concomitant medications for IMDELLTRA during Cycle 1 Day 1 and Cycle 1 Day 8 as presented in Table 3 to reduce the risk of CRS *[see Warnings and Precautions (5.1)]*.

Table 3. Recommended Concomitant Medications for IMDELLTRA Administration for Cycle 1 Day 1 and Cycle 1 Day 8

Treatment Day	Medication	Administration
Cycle 1 Day 1 and Cycle 1 Day 8	Administer dexamethasone 8 mg intravenously (or equivalent)	Within 1 hour prior to IMDELLTRA administration
	Administer 1 liter of normal saline intravenously over 2 to 4 hours	Immediately after completion of IMDELLTRA infusion

2.4 Restarting IMDELLTRA After Dosage Delay

If a dose of IMDELLTRA is delayed, restart based on the recommendation as listed in Table 4 and resume the dose and schedule accordingly *[see Dosage and Administration (2.2)]*.

Administer recommended concomitant medications as indicated in Table 3.

Table 4. Recommendations for Restarting IMDELLTRA After Dosage Delay

Last Dose Administered	Time Since the Last Dose Administered	Action[a]
1 mg on Cycle 1 Day 1	2 weeks or less (≤ 14 days)	Administer IMDELLTRA 10 mg, then resume with the planned dose and schedule.
	Greater than 2 weeks (> 14 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dose and schedule.
10 mg on Cycle 1 Day 8	3 weeks or less (≤ 21 days)	Administer IMDELLTRA 10 mg, then resume with the planned dose and schedule.
	Greater than 3 weeks (> 21 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dose and schedule.

10 mg on Cycle 1 Day 15 and subsequent Cycles every 2 weeks thereafter	4 weeks or less (≤ 28 days)	Administer IMDELLTRA 10 mg, then resume with the planned dose and schedule.
	Greater than 4 weeks (> 28 days)	Administer IMDELLTRA step-up dose 1 mg. If tolerated, increase to 10 mg 1 week later. Then resume with the planned dose and schedule.

a. Administer recommended concomitant medications before and after Cycle 1 Day 1 and Cycle 1 Day 8 IMDELLTRA infusions and monitor patients accordingly *[see Dosage and Administration (2.1, 2.2 and 2.3)]*.

2.5 IMDELLTRA Dosage Modifications and Adverse Reaction Management

No dose reduction for IMDELLTRA is recommended. See Table 5 and Table 6 for recommended management of CRS, neurologic toxicity including ICANS respectively and Table 7 for cytopenias, infections and other adverse reactions.

Cytokine Release Syndrome (CRS)

Diagnose CRS based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia, and hypotension.

If CRS is suspected, manage according to the recommendations in Table 5. Monitor patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygen) with continuous cardiac telemetry and pulse oximetry.

For severe or life-threatening CRS, recommend administering tocilizumab or equivalent therapy and intensive monitoring (e.g., ICU) for supportive therapy. Perform laboratory testing to monitor for disseminated intravascular coagulation (DIC), hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function. Table 5 provides the guidelines for grading and dosage modification and management of cytokine release syndrome.

Table 5. Guidelines for Grading and Dosage Modification and Management of Cytokine Release Syndrome[a]

CRS Grade	Defining Symptoms	IMDELLTRA Dosage Modification	Management
Grade 1	Symptoms require symptomatic treatment only (e.g., fever ≥ 100.4°F without hypotension or hypoxia).	Withhold IMDELLTRA until event resolves, then resume IMDELLTRA at the next scheduled dose[b].	• Administer symptomatic treatment (e.g., acetaminophen) for fever. • Consider dexamethasone 4 mg to 10 mg oral or IV (or equivalent)[c].
Grade 2	Symptoms require and	Withhold IMDELLTRA until	• Recommend hospitalization for a minimum of 24 hours with

CRS Grade	Defining Symptoms	IMDELLTRA Dosage Modification	Management
	respond to moderate intervention. Fever ≥ 100.4°F, • Hypotension responsive to fluids not requiring vasopressors and/or • Hypoxia requiring low flow nasal cannula or blow-by.	event resolves, then resume IMDELLTRA at the next scheduled dose[b].	cardiac telemetry and pulse oximetry. • Administer symptomatic treatment (e.g., acetaminophen) for fever. • Administer supplemental oxygen and intravenous fluids when indicated. • Consider dexamethasone[c] (or equivalent) 8 mg oral or IV. • Consider tocilizumab (or equivalent). When resuming the next planned dose, monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours in an appropriate healthcare setting[b].
Grade 3	Severe symptoms defined as temperature ≥ 100.4°F with: • Hemodynamic instability requiring a vasopressor (with or without vasopressin) and/or • Worsening hypoxia or respiratory distress requiring high flow nasal cannula (> 6 L/min oxygen) or face mask.	Withhold IMDELLTRA until the event resolves, then resume IMDELLTRA at the next scheduled dose[b]. For recurrent Grade 3 events, permanently discontinue IMDELLTRA.	In addition to Grade 2 treatment: • Recommend intensive monitoring, e.g., ICU care. • Administer dexamethasone[c] (or equivalent) 8 mg IV every 8 hours up to 3 doses. • Vasopressor support as needed. • High flow oxygen support as needed. • Recommend tocilizumab (or equivalent). Prior to the next dose, administer concomitant medications as recommended for Cycle 1 Day 1 and Cycle 1 Day 8 (see Table 3). When resuming the next planned dose, monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours in an appropriate healthcare setting[b].

CRS Grade	Defining Symptoms	IMDELLTRA Dosage Modification	Management
Grade 4	Life-threatening symptoms defined as temperature ≥ 100.4°F with: • Hemodynamic instability requiring multiple vasopressors (excluding vasopressin). and/or Worsening hypoxia or respiratory distress despite oxygen administration requiring positive pressure.	Permanently discontinue IMDELLTRA.	• ICU care. • Per Grade 3 treatment. Recommend tocilizumab (or equivalent)

[a] CRS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019).
[b] See Table 4 for recommendations on restarting IMDELLTRA after dose delays *[see Dosage and Administration (2.4)]*.
[c] Taper steroids per standard of care guidelines.

Neurologic Toxicity including ICANS

At the first sign of neurologic toxicity, including ICANS, withhold IMDELLTRA and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for severe or life-threatening neurologic toxicities, including ICANS *[see Warnings and Precautions (5.2)]*. Manage ICANS and neurologic toxicity according to the recommendations in Table 6 and consider further management per current practice guidelines.

Table 6. Guidelines for Management of Neurologic Toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)[a]

ICANS Grade[a]	Defining Symptoms	IMDELLTRA Dosage Modifications	Management
Grade 1	ICE score 7-9[b] with no depressed level of consciousness.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c].	• Supportive care.
Grade 2	ICE score 3-6[b] and/or mild somnolence awaking to voice.	• Withhold IMDELLTRA until ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c].	• Supportive care. • Dexamethasone[d] (or equivalent) 8 to 10 mg oral or IV. Can repeat every 12 hours or methylprednisolone[d] (or equivalent) 1 mg/kg IV every 12 hours if symptoms worsen. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. • Monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours following the next dose of IMDELLTRA.
Grade 3	ICE score 0-2[b] and/or depressed level of consciousness awakening only to tactile stimulus and/or any clinical seizure focal or generalized	• Withhold IMDELLTRA until the ICANS resolves, then resume IMDELLTRA at the next scheduled dose[c]. • If there is no improvement to Grade ≤ 1 within 7 days permanently discontinue IMDELLTRA.	• Recommend intensive monitoring, e.g., ICU care. • Consider mechanical ventilation for airway protection. Dexamethasone[d] (or equivalent) 10 mg IV every

ICANS Grade[a]	Defining Symptoms	IMDELLTRA Dosage Modifications	Management
	that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention and/or Focal or local edema on neuroimaging.	• For recurrent Grade 3 events, permanently discontinue IMDELLTRA.	6 hours or methylprednisolone[d] (or equivalent) 1 mg/kg IV every 12 hours. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity. Monitor patients from the start of the IMDELLTRA infusion for 22 to 24 hours following the next dose of IMDELLTRA.
Grade 4	ICE score 0[b] (patient is unarousable and unable to perform ICE) and/or Stupor or coma and/or Life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between and/or diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema,	• Permanently discontinue IMDELLTRA.	• ICU care. • Consider mechanical ventilation for airway protection. • High dose corticosteroids (e.g., methylprednisolone[d] 1000 mg/day in divided doses IV for 3 days). • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.

ICANS Grade[a]	Defining Symptoms	IMDELLTRA Dosage Modifications	Management
	cranial nerve VI palsy, or Cushing's triad.		

a. ICANS based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (2019)
b. If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (names 3 objects, e.g., point to clock, pen, button = 3 points); Following commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points
c. See **Table 4** for recommendations on restarting IMDELLTRA after dose delays *[see Dosage and Administration (2.4)]*
d. Taper steroids per standard of care guidelines

Table 7. Recommended Treatment Interruptions of IMDELLTRA for the Management of Cytopenias, Infections, and Other Adverse Reactions

Adverse Reactions	Severity[b]	Dosage Modification[a]
Cytopenias *[see Warnings and Precautions (5.3)]*	Grade 3 Neutropenia	Withhold IMDELLTRA until recovery to Grade ≤ 2. Consider administration of granulocyte colony stimulating factor (G-CSF). Permanently discontinue if recovery to Grade ≤ 2 does not occur within 3 weeks.
	Grade 4 Neutropenia	Withhold IMDELLTRA until recovery to Grade ≤ 2. Consider administration of granulocyte colony stimulating factor (G-CSF). Permanently discontinue if recovery to Grade ≤ 2 does not occur within 1 week.
	Recurrent Grade 4 Neutropenia	Permanently discontinue IMDELLTRA
	Febrile neutropenia	Withhold IMDELLTRA until neutropenia recovers to

Adverse Reactions	Severity[b]	Dosage Modification[a]
		Grade ≤ 2 and fever resolves.
	Hemoglobin <8 g/dL	Withhold IMDELLTRA until hemoglobin is ≥8 g/dL.
	Grade 3 or Grade 4 Decreased platelet count	Withhold IMDELLTRA until platelet count is Grade ≤ 2 and no evidence of bleeding. Permanently discontinue if recovery to Grade ≤ 2 does not occur within 3 weeks.
	Recurrent Grade 4 Decreased platelet count	Permanently discontinue IMDELLTRA.
Infections *[see Warnings and Precautions (5.4)]*	All Grades	Withhold IMDELLTRA in the step-up phase in patients until infection resolves.
	Grade 3	Withhold IMDELLTRA during the treatment phase until infection improves to Grade ≤ 1[a].
	Grade 4	Permanently discontinue IMDELLTRA.
Hepatotoxicity *[see Warnings and Precautions (5.5)]*	Grade 3 Increased ALT or AST or bilirubin	Withhold IMDELLTRA until improved to Grade ≤ 1.
	Grade 4 Increased ALT or AST or bilirubin	Permanently discontinue IMDELLTRA.
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	Permanently discontinue IMDELLTRA.

Adverse Reactions	Severity[b]	Dosage Modification[a]
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or 4	Withhold IMDELLTRA until recovery to Grade ≤ 1 or baseline. Consider permanently discontinuing if adverse reaction does not resolve within 28 days. Consider permanent discontinuation for Grade 4 events.

[a] Refer to Table 4 for dose restarting guidance.
[b] Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

2.6 Preparation

Material Compatibility Information

- IV bags composed of ethyl vinyl acetate (EVA), polyolefin, and polyvinyl chloride (PVC) have been shown to be compatible with IMDELLTRA at the specified administration conditions.
- IV line and catheter materials composed of polyolefin, PVC, and polyurethane have been shown to be compatible with IMDELLTRA at the specified administration conditions.
- The use of Closed System Transfer Device (CSTD) is not recommended due to potential wrong dose medication error risk. Amgen has not performed compatibility testing of vial adaptor CSTDs with IMDELLTRA.

Step 1: Reconstitute IMDELLTRA with Sterile Water for Injection

- Table 8 provides the required amount of sterile water for injection required to reconstitute IMDELLTRA 1 mg and 10 mg vials.

Do not use IV Solution Stabilizer (IVSS) to reconstitute IMDELLTRA.

The IV Solution Stabilizer (IVSS) is used to coat the intravenous bag prior to addition of reconstituted IMDELLTRA to prevent adsorption of IMDELLTRA to IV bags and IV tubing.

Table 8. Required Amount of Sterile Water for Injection to Reconstitute IMDELLTRA[a]

IMDELLTRA Vial Strength	Amount of Sterile Water for Injection Needed to Reconstitute IMDELLTRA	Resulting Concentration

1 mg	1.3 mL	0.9 mg/mL
10 mg	4.4 mL	2.4 mg/mL

[a] Each vial contains overfill to allow for withdrawal of 1.1 mL (1 mg vial) or 4.2 mL (10 mg vial) after reconstitution to ensure delivery at the stated concentration of labeled vial strength.

- Using a needle and syringe filled with the required amount of sterile water, inject the sterile water against the glass vial. Avoid injecting the water directly onto the powder to prevent foaming.
- Gently swirl the contents to mix. Do not shake.
- Inspect parenteral drug products for particulate matter and discoloration prior to administration. Inspect that the solution is clear to opalescent, colorless to slightly yellow. Do not use if the solution is cloudy or has particulates.
- Further dilute reconstituted IMDELLTRA.
- The reconstituted IMDELLTRA must be further diluted within 4 hours of reconstitution or discarded.

Prepare the infusion bag: Steps 2 to 5

Step 2: Withdraw 0.9% Sodium Chloride for Injection

- Using a 250 mL prefilled bag of 0.9% Sodium Chloride for Injection, withdraw the amount of sodium chloride specified in Table 9 and discard.

Table 9. Required Amount of 0.9% Sodium Chloride to Withdraw from 250 mL IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of 0.9% Sodium Chloride to Withdraw From 250 mL IV Bag
1 mg	1 mg	14 mL
10 mg	10 mg	17 mL

Step 3: Add IV Solution Stabilizer to the infusion bag

- Inject 13 mL of IV Solution Stabilizer (IVSS) into the 250 mL 0.9% Sodium Chloride infusion bag, see Table 10.
- Gently mix the contents of the infusion bag to avoid foaming. Do not shake.

Table 10. Required Amount of IV Solution Stabilizer (IVSS) to Add to IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of IV Solution Stabilizer (IVSS) to Add to IV Bag
1 mg	1 mg	13 mL
10 mg	10 mg	13 mL

Step 4: Dilute the reconstituted IMDELLTRA into the infusion bag

- Transfer the required volume of reconstituted IMDELLTRA listed in Table 11 to the infusion bag *(containing IV Solution Stabilizer)*.

NOTE: The final concentrations for the different strength vials are NOT the same following reconstitution and further dilution.

Table 11. Required Amount of Reconstituted IMDELLTRA to Add to 250 mL IV Bag

IMDELLTRA Vial Strength	IMDELLTRA Dose	Volume of Reconstituted IMDELLTRA to Add to 250 mL IV Bag
1 mg	1 mg	1.1 mL
10 mg	10 mg	4.2 mL

- Gently mix the contents of the bag. Do not shake.

Step 5: Remove air from IV bag

Remove air from the prepared IV bag using an empty syringe to avoid foaming.

Step 6: Prime IV tubing

- Prime intravenous tubing with either 0.9% Sodium Chloride for Injection or with the final prepared product.
- See Table 12 for maximum storage time of prepared IMDELLTRA infusion.

Prepared IMDELLTRA Infusion Bag Storage Requirements

- Administer reconstituted and diluted IMDELLTRA immediately.
- Table 12 displays the maximum storage time for the prepared IMDELLTRA infusion bag.
- Maximum storage time includes total duration from the time of reconstitution of the vial of IMDELLTRA to the end of the infusion.

Table 12. Maximum Storage Time for Prepared IMDELLTRA Infusion Bag

	Room Temperature 20°C to 25°C (68°F to 77°F)	Refrigerated 2°C to 8°C (36°F to 46°F)
Prepared IMDELLTRA Infusion Bag	8 hours	7 days

- Discard the prepared IMDELLTRA infusion bag after maximum storage time (from time of reconstitution).
- If refrigerated, allow the prepared IMDELLTRA infusion bag to come room temperature prior to administration, and complete the infusion within 8 hours (including preparation and infusion time).
- Do not re-refrigerate prepared infusion bag.

3 DOSAGE FORMS AND STRENGTHS

For injection: 1 mg of white to slightly yellow lyophilized powder in a single-dose vial for reconstitution and further dilution.

For injection: 10 mg of white to slightly yellow lyophilized powder in a single-dose vial for reconstitution and further dilution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

IMDELLTRA can cause cytokine release syndrome (CRS) including life-threatening or fatal reactions.

In the pooled safety population *[see Adverse Reactions (6.1)]*, CRS occurred in 57% (268/473) of patients who received IMDELLTRA, including 39% Grade 1, 15% Grade 2, 1.7% Grade 3 and 0.2% Grade 4. Recurrent CRS occurred in 24% of IMDELLTRA-treated patients including 20% Grade 1 and 3.4% Grade 2; one patient experienced recurrent Grade 3.

Among the 268 patients who experienced CRS, 73% had CRS after the first dose, 60% had CRS after the second dose, and 15% had CRS following the third or later dose. Following the Cycle 1 Day 1, Day 8, Day 15 infusions, 24%, 8%, and 1% of patients experienced Grade ≥ 2 CRS, respectively. From Cycle 2 onwards, 1.5% of patients experienced Grade ≥ 2 CRS. Of the patients who experienced CRS, 31% received steroids and 10% required tocilizumab. The median time to onset of all grade CRS from most recent dose of IMDELLTRA was 16 hours (range: start of infusion to 15 days). The median time to onset of Grade ≥ 2 CRS from most recent dose of IMDELLTRA was 15 hours (range: start of infusion to 15 days).

Clinical signs and symptoms of CRS included pyrexia, hypotension, fatigue, tachycardia, headache, hypoxia, nausea and vomiting. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Administer IMDELLTRA following the recommended step-up dosing and administer concomitant medications before and after Cycle 1 Day 1 and Cycle 1 Day 8 IMDELLTRA infusions as described in Table 3 to reduce the risk of CRS *[see Dosage and Administration (2.3)]*. Administer IMDELLTRA in an appropriate healthcare facility equipped to monitor and manage CRS. Ensure patients are well hydrated prior to administration of IMDELLTRA.

Closely monitor patients for signs and symptoms of CRS during treatment with IMDELLTRA. At the first sign of CRS, immediately discontinue IMDELLTRA infusion, evaluate the patient for hospitalization and institute supportive care based on severity. Withhold or permanently discontinue IMDELLTRA based on severity *[see Dosage and Administration (2.5)]*. Counsel patients and caregivers to seek medical attention should signs or symptoms of CRS occur.

5.2 Neurologic Toxicity Including ICANS

IMDELLTRA can cause life-threatening or fatal neurologic toxicity including ICANS.

In the pooled safety population *[see Adverse Reactions (6.1)]*, neurologic toxicity occurred in 65% of patients who received IMDELLTRA, with Grade 3 or higher events in 7% of patients including fatal events in 0.2%. The most frequent neurologic toxicities were dysgeusia (34%), headache (17%), peripheral neuropathy (9%), dizziness (9%), and insomnia (8%).

The incidence of signs and symptoms consistent with ICANS was 10% in IMDELLTRA-treated patients, including events with the preferred terms: ICANs (4.7%), muscular weakness (3.2%), cognitive disorder (0.6%), aphasia (0.6%), depressed level of consciousness (0.4%), seizures (0.4%), encephalopathy (0.4%), and leukoencephalopathy (0.2%). There was one fatal reaction of ICANS *[see Adverse Reactions (6.1)]*. Recurrent ICANS occurred in 1.5% of patients. Of the patients who experienced ICANS, most experienced the event following Cycle 1 Day 1 (2.5%) and Cycle 1 Day 8 (3.6%). Following Day 1, Day 8, and Day 15 infusions, 1.3%, 1.3% and 0.4% of patients experienced Grade ≥ 2 ICANS, respectively. ICANS can occur several weeks following administration of IMDELLTRA. The median time to onset of ICANS from the first dose of IMDELLTRA was 16 days (range: 1 to 862 days). The median time to resolution of ICANS was 4 days (range: 1 to 40 days).

The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.

Patients receiving IMDELLTRA are at risk of neurologic adverse reactions and ICANS resulting in depressed level of consciousness. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until neurologic symptoms resolve.

Closely monitor patients for signs and symptoms of neurologic toxicity and ICANS during treatment with IMDELLTRA. At the first sign of ICANS, immediately discontinue the infusion, evaluate the patient and provide supportive therapy based on severity.

Withhold IMDELLTRA or permanently discontinue based on severity *[see Dosage and Administration (2.5)]*.

5.3 Cytopenias

IMDELLTRA can cause cytopenias including neutropenia, thrombocytopenia, and anemia.

In the pooled safety population, *[see Adverse Reactions (6.1)]* based on laboratory data, decreased neutrophils occurred in 16% of patients, including 9% Grade 3 or 4. The median time to onset for Grade 3 or 4 decreased neutrophil count was 41 days (range: 2 to 306 days). Decreased platelets occurred in 30%, including 2.2% Grade 3 or 4. The median time to onset for Grade 3 or 4 decreased platelets was 67 days (range: 3 to 420 days). Decreased hemoglobin occurred in 56% of patients, including 4.7% Grade 3 or 4.

Febrile neutropenia was reported as an adverse event in 1.5% of patients treated with IMDELLTRA.

Monitor patients for signs and symptoms of cytopenias. Perform complete blood counts prior to treatment with all doses of IMDELLTRA, up through Cycle 5 Day 15 and then prior to administration of IMDELLTRA on Day 1 of each cycle starting with Cycle 6. Based on the severity of cytopenias, temporarily withhold or permanently discontinue IMDELLTRA *[see Dosage and Administration (2.5)]*.

5.4 Infections

IMDELLTRA can cause serious infections, including life-threatening and fatal infections.

In the pooled safety population, *[see Adverse Reactions (6.1)]*, infections including opportunistic infections occurred in 43% of patients who received IMDELLTRA, including 14% Grade 3 or 4. The most frequent infections were pneumonia (11%), urinary tract infection (9%), COVID-19 (6%), upper respiratory tract infection (4.7%), respiratory tract infection (4%), candida infection (2.1%), oral candidiasis (2.1%) and nasopharyngitis (2.1%).

Monitor patients for signs and symptoms of infection prior to and during treatment with IMDELLTRA and treat as clinically indicated. Withhold or permanently discontinue IMDELLTRA based on severity *[see Dosage and Administration (2.5)]*.

5.5 Hepatotoxicity

IMDELLTRA can cause hepatotoxicity.

In the pooled safety population *[see Adverse Reactions (6.1)]*, based on laboratory data, elevated ALT occurred in 39% of patients who received IMDELLTRA, including 2.5% Grade 3 or 4 ALT. Elevated AST occurred in 43% of patients, including 3.2% Grade 3 or 4. Elevated bilirubin occurred in 16% of patients, including 1.3% Grade 3 or 4 *[see Adverse Reactions (6.1)]*. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin prior to treatment with IMDELLTRA, and as clinically indicated. Withhold IMDELLTRA or permanently discontinue based on severity *[see Dosage and Administration (2.5)]*.

5.6 Hypersensitivity

IMDELLTRA can cause severe hypersensitivity reactions.

Clinical signs and symptoms of hypersensitivity may include, but are not limited to, rash and bronchospasm.

Monitor patients for signs and symptoms of hypersensitivity during treatment with IMDELLTRA and manage as clinically indicated. Withhold or consider permanent discontinuation of IMDELLTRA based on severity *[see Dosage and Administration (2.5)]*.

5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, IMDELLTRA may cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome (CRS) *[see Warnings and Precautions (5.1)]*
- Neurologic Toxicity Including ICANS *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Infections *[see Warnings and Precautions (5.4)]*
- Hepatotoxicity *[see Warnings and Precautions (5.5)]*
- Hypersensitivity *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to intravenous IMDELLTRA, as a single agent, at the recommended dosage of IMDELLTRA 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8 and 15, and then every 2 weeks until disease progression or intolerable toxicity in 473 patients with small cell lung cancer enrolled in three clinical trials: DeLLphi-300, DeLLphi-301 and DeLLphi-304. Among 473 patients who received IMDELLTRA, 40% were exposed for 6 months or longer and 19% were exposed for greater than one year. The most common (≥ 20%) adverse reactions were CRS (57%), fatigue (48%), decreased appetite (38%), dysgeusia (34%), pyrexia (33%), constipation (31%), musculoskeletal pain (31%), and nausea (25%). The most common (≥ 5%) Grade 3 or 4 laboratory

abnormalities were decreased lymphocytes (43%), decreased sodium (12%), decreased total neutrophils (9%), and increased uric acid (6%).

Extensive Stage Small Cell Lung Cancer

The safety of IMDELLTRA was evaluated in 252 patients in DeLLphi-304, a multicenter, randomized, open label trial in patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression following treatment with platinum-based chemotherapy with or without an anti-PD-(L)1 antibody *[see Clinical Studies (14.1)].* Patients received IMDELLTRA (n=252) or investigator's choice or investigator's choice of topotecan [n=176], lurbinectedin [n=45] or amrubicin [n=23].

Among patients who received IMDELLTRA, 41% were exposed for 6 months or longer and 18% were exposed for greater than one year.

The demographic characteristics of patients who received IMDELLTRA were: median age 64 years (range: 20 to 86); 71% male; 60% White, 38 % Asian, 0.8% Black or African American; and 4.8% were of Hispanic or Latino ethnicity.

Serious adverse reactions occurred in 52% of patients who received IMDELLTRA. Serious adverse reactions in >3% of patients included CRS (17%), pyrexia (6%), pneumonia (5%) and ICANS (3.6%). Fatal adverse reactions occurred in 8% of patients who received IMDELLTRA, including one fatal adverse reaction of ICANS (0.4%). Fatal adverse reactions occurring in more than one patient included pneumonia (1.6%), cardio-respiratory arrest (1.6%), and sepsis (0.8%).

Permanent discontinuation of IMDELLTRA due to an adverse reaction occurred in 6% of patients. Adverse reactions which resulted in permanent discontinuation of IMDELLTRA in > 1% of patients included pneumonia (1.2%).

Dosage interruptions of IMDELLTRA due to an adverse reaction occurred in 38% of patients. Adverse reactions which required dosage interruption in ≥ 2% of patients included neutropenia (5%), fatigue (4.4%), pneumonia (4%), decreased appetite (2.8%), COVID-19 (2%).

Table 13 summarizes adverse reactions observed in DeLLphi-304.

Table 13. Adverse Reactions (≥ 15%) in Patients with SCLC Who Received IMDELLTRA in DeLLphi-304

Adverse Reaction	IMDELLTRA[a] (N = 252)		Standard of Care (N = 244)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Immune system disorders				
Cytokine release syndrome[b]	56	1.2	1.2	0
General disorders and administration site conditions				

Adverse Reaction	IMDELLTRA[a] (N = 252)		Standard of Care (N = 244)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Fatigue[c]	39	6	43	10
Pyrexia[d]	29	1.2	11	1.2
Metabolism and nutrition disorders				
Decreased appetite	37	2	23	1.6
Gastrointestinal disorders				
Constipation	30	0.4	22	0
Nausea	25	0.4	32	0
Nervous system disorders				
Dysgeusia[e]	28	0	2.5	0
Headache[f]	16	0	9	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[g]	27	1.6	21	2.5
Respiratory, thoracic and mediastinal disorders				
Cough[h]	17	0	17	0

[a] Graded using CTCAE Version 4.0 and Version 5.0.
[b] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019.
[c] Includes fatigue and asthenia
[d] Includes body temperature increased, hyperthermia, pyrexia
[e] Includes ageusia, dysgeusia, hypogeusia
[f] Includes headache and tension headache
[g] Includes arthralgia, back pain, bone pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
[h] Includes cough and productive cough

Clinically relevant adverse reactions occurring in < 15% of patients who received IMDELLTRA were immune effector cell-associated neurotoxicity syndrome, neurotoxicity, tremor, seizure, ataxia, confusional state, delirium, dyspnea, encephalopathy and weight decreased.

Table 14 summarizes laboratory abnormalities in DeLLphi-304.

Table 14. Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with SCLC in DeLLphi-304

Laboratory Abnormality	IMDELLTRA[a] N=252		Standard of care N=244	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Lymphocytes decreased	65	27	62	27

Laboratory Abnormality	IMDELLTRA[a] N=252		Standard of care N=244	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hemoglobin decreased	51	4.5	86	29
White blood cells decreased	50	7	70	29
Platelets decreased	25	0.4	55	20
Neutrophils decreased[b]	15	10	44	36
Chemistry				
Sodium decreased	57	8	38	7
Potassium decreased	41	4.8	34	4
Aspartate amino transferase increased	40	2.8	29	0.4
Sodium increased	35	0.4	27	0
Alanine aminotransferase increased	32	2	25	0.9
Activated Partial Thromboplastin Time (sec) increased	26	1.3	16	0.9
Creatinine increased	23	0.8	19	0.4
Alkaline phosphate increased	22	0.4	26	1.4
Magnesium decreased	21	0.8	15	1.8
Potassium increased	21	0.8	12	1.8
Creatine Phosphokinase increased	21	1.7	11	0

[a] The denominator used to calculate the rate varied for IMDELLTRA (Range: 229 to 250) and SOC (Range: 205 to 226) based on the number of patients with a baseline value and at least one post-treatment value.
[b] All Grade lab abnormalities occurring at a frequency less than 20% included decreased neutrophils.

DeLLphi-300 and DeLLphi-301

The safety of IMDELLTRA, as a single agent, at the recommended dosage was evaluated in patients with extensive stage small cell lung cancer enrolled in DeLLphi-300 and DeLLphi-301 *[see Clinical Studies (14.1)].* Among 187 patients who received IMDELLTRA, 31% were exposed for 6 months or longer and 14% were exposed for greater than one year.

The demographic characteristics of patients who received IMDELLTRA were: median age 66 years (range: 35 to 82); 65% male; 70% White, 26% Asian, 2.1% Black or African American; and 2.1% Hispanic or Latino.

Serious adverse reactions occurred in 58% of patients who received IMDELLTRA. Serious adverse reactions in >3% of patients included cytokine release syndrome (24%), pneumonia (6%), pyrexia (3.7%) and hyponatremia (3.6%). Fatal adverse reactions occurred in 2.7% of patients who received IMDELLTRA including pneumonia 0.5%, aspiration (0.5%), pulmonary embolism (0.5%), respiratory acidosis (0.5%), and respiratory failure (0.5%).

Permanent discontinuation of IMDELLTRA due to an adverse reaction occurred in 7% of patients. Adverse reactions which resulted in permanent discontinuation of IMDELLTRA in >1% of patients included cytokine release syndrome (1.6%) and tumor lysis syndrome (1.1%).

Dosage interruptions of IMDELLTRA due to an adverse reaction occurred in 27% of patients. Adverse reactions which required dosage interruption in ≥ 2% of patients included fatigue (3.2%), cytokine release syndrome (2 .7%) and respiratory tract infection (2.1%).

Table 15 summarizes adverse reactions observed in DeLLphi-300 and DeLLphi-301.

Table 15. Adverse Reactions (≥ 15%) in Patients with ES-SCLC Who Received IMDELLTRA in DeLLphi-300 and DeLLphi-301

Adverse Reaction	**IMDELLTRA* (N = 187)**	
	Any Grade (%)	**Grade 3 or 4 (%)**
Immune system disorders		
Cytokine release syndrome†	55	1.6
General disorders and administration site conditions		
Fatigue‡	51	10
Pyrexia	36	0
Nervous system disorders		
Dysgeusia	36	0
Metabolism and nutrition disorders		
Decreased appetite	34	2.7
Nausea	22	1.6
Gastrointestinal disorders		
Constipation	30	0.5
Musculoskeletal and connective tissue disorders		

Musculoskeletal pain§	30	1.1
Respiratory, thoracic and mediastinal disorders		
Dyspnea¶	17	2.1
Cough	17	0

*Graded using CTCAE Version 4.0 and Version 5.0.
†Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019.
‡Includes fatigue and asthenia.
§Includes myalgia, arthralgia, back pain, pain in extremity, neck pain, musculoskeletal chest pain, non-cardiac chest pain and bone pain.
¶Includes dyspnea and exertional dyspnea.

Table 16 summarizes laboratory abnormalities in DeLLphi-300 and DeLLphi-301

	IMDELLTRA*	
	All Grades (%)	**Grade 3 or 4 (%)**
Laboratory Abnormality		
Hematology		
Lymphocytes decreased	84	57
Hemoglobin decreased	58	5
White blood cells decreased	44	3.8
Platelets decreased	33	3.2
Neutrophils decreased†	12	6
Chemistry		
Sodium decreased	68	16
Potassium decreased	50	5
Aspartate amino transferase increased	44	3.2
Alanine aminotransferase increased	42	2.1
Magnesium decreased	33	1.6
Creatinine increased	29	0.5
Sodium increased	26	0
Alkaline phosphate increased	22	0

*The denominator used to calculate the rate varied from 41 to 187 based on the number of patients with a baseline value and at least one post-treatment value.

†All Grade lab abnormalities occurring at a frequency less than 20% included decreased neutrophils.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, IMDELLTRA may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no

available data on the use of IMDELLTRA in pregnant women to inform a drug-associated risk.

In an animal reproduction study, a murine surrogate molecule administered intravenously to pregnant mice crossed the placental barrier.

Tarlatamab-dlle causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance.

Human immunoglobulin G (IgG) and proteins comprising IgG-derived fragment crystallizable (Fc) domains are known to cross the placental barrier; therefore, IMDELLTRA has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with tarlatamab-dlle. In an embryo-fetal developmental toxicity study, a murine surrogate molecule was administered intravenously to pregnant mice during the period of organogenesis. The surrogate molecule crossed the placental barrier and did not cause maternal toxicity, embryo-fetal toxicity or teratogenicity.

8.2 Lactation

Risk Summary

There are no data on the presence of tarlatamab-dlle in human milk or the effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to IMDELLTRA are unknown. Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with IMDELLTRA and for 2 months after the last dose.

8.3 Females and Males of Reproductive Potential

IMDELLTRA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating IMDELLTRA.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of IMDELLTRA have not been established in pediatric patients.

8.5 Geriatric Use

Of the 473 patients with SCLC who received IMDELLTRA 10 mg as a single agent, 51% were 65 years of age or older and 11% were 75 years of age or older. No overall differences in IMDELLTRA pharmacokinetics, safety or efficacy were observed between older patients (≥ 65 years of age) and younger patients.

11 DESCRIPTION

Tarlatamab-dlle is a bispecific DLL3-directed CD3 T-cell engager that binds to DLL3 expressed on the surface of cells, including tumor cells, and CD3 expressed on the surface of T cells. Tarlatamab-dlle is produced using recombinant DNA technology in Chinese hamster ovary cells. It consists of 982 amino acids and has a molecular weight of approximately 105 kilodaltons.

IMDELLTRA (tarlatamab-dlle) for injection is supplied as a sterile, preservative-free, white to slightly yellow, lyophilized powder in a single-dose vial for reconstitution and further dilution.

Each 1 mg vial contains tarlatamab-dlle (1 mg), glutamic acid (0.72 mg), polysorbate 80 (0.04 mg), sucrose (37.1 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 1.3 mL of Sterile Water for Injection the resulting concentration is 0.9 mg/mL IMDELLTRA.

Each 10 mg vial contains tarlatamab-dlle (10 mg), glutamic acid (3.7 mg), polysorbate 80 (0.2 mg), sucrose (194.4 mg), and sodium hydroxide to adjust pH to 4.2. After reconstitution with 4.4 mL of Sterile Water for Injection the resulting concentration is 2.4 mg/mL IMDELLTRA.

IV Solution Stabilizer is supplied as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each vial of IV Solution Stabilizer contains citric acid monohydrate (36.75 mg), lysine hydrochloride (1598.8 mg), polysorbate 80 (7 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tarlatamab-dlle is a bispecific T-cell engager that binds to DLL3 expressed on the surface of cells, including tumor cells, and CD3 expressed on the surface of T cells. Tarlatamab-dlle causes T-cell activation, release of inflammatory cytokines, and lysis of DLL3-expressing cells. Tarlatamab-dlle had anti-tumor activity in mouse models of SCLC.

12.2 Pharmacodynamics

Exposure-Response Relationships

There are no clinically significant exposure-response relationships for efficacy over the exposure range observed between tarlatamab-dlle 10 mg and 100 mg (10 times the highest approved recommended dosage).

There is an exposure-response relationship between tarlatamab-dlle exposure and neutropenia or neurologic toxicity including ICANS with a higher risk of any grade neutropenia or neurologic toxicity including ICANS at higher exposure.

Serum Cytokines

Transient elevation of serum cytokines IL-2, IL-6, IL-8, IL-10, and IFN-γ were observed at a tarlatamab-dlle dosage of 0.3 mg and above. Peak elevation of cytokines was generally observed 24 hours following the initial dose of IMDELLTRA at 1 mg on Cycle 1 Day 1 and generally returned to baseline levels prior to the next infusion on Cycle 1 Day 8.

12.3 Pharmacokinetics

Tarlatamab-dlle pharmacokinetic data in patients with SCLC at the approved recommended dosage are presented as mean (CV%) unless otherwise specified. The exposure of tarlatamab-dlle increases in a dose proportional manner over the dosage range of 1 mg to 100 mg (10 times the highest approved recommended dosage) every 2 weeks. Tarlatamab-dlle steady state is achieved by Cycle 2 Day 15. Pharmacokinetic parameters are summarized for the recommended dosage of IMDELLTRA in Table 17.

Table 17. Pharmacokinetic Parameters of Tarlatamab-dlle

	Parameter		
	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
First step-up dose 1 mg	106 (26%)	314 (35%)	49 (35%)
First treatment dose 10 mg	1,100 (26%)	3,190 (35%)	517 (36%)
Steady state 10 mg every 2 weeks	1,040 (37%)	3,640 (35%)	472 (62%)

Distribution

Tarlatamab-dlle steady state volume of distribution is 8.5 L (33%).

Metabolism

Tarlatamab-dlle is expected to be metabolized into small peptides by catabolic pathways.

Elimination

Tarlatamab-dlle terminal elimination half-life is 11 days (31%) with an estimated systemic clearance of 0.7 L/day (34%).

Specific Populations

No clinically significant differences in the pharmacokinetics of tarlatamab-dlle were observed based on age (20 to 86 years), body weight (35 to 149 kg), sex, race (68% White and 27% Asian), mild or moderate renal impairment (eGFR 30 to < 90 mL/min), or mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN).

The effects of severe renal impairment (eGFR 15 to < 30 mL/min), end-stage renal disease (eGFR <15 mL/min), or moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and any AST) on the pharmacokinetics of tarlatamab-dlle are unknown.

Effects of Tarlatamab-dlle on CYP450 Substrates

Tarlatamab-dlle causes transient release of cytokines that may suppress CYP450 enzymes and may result in an increased exposure of concomitant CYP substrates during and up to 14 days after occurrence of cytokine release syndrome *[see Clinical Pharmacology (12.2)]*.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of tarlatamab-dlle or of other tarlatamab products.

During the maximum 3-year treatment period during which the presence of ADA was evaluated in DeLLphi-300, DeLLphi-301, and DeLLphi-304, 8% (36/445) of patients who received the recommended step-up and full dose of IMDELLTRA developed treatment-emergent ADA. In DeLLphi-301 and DeLLphi-304, which included neutralizing antibody assessments, 38% (11/29) of the patients who developed treatment-emergent ADA also developed neutralizing antibodies. ADA resulted in a 14% increase in the clearance of tarlatamab-dlle. Because of the low occurrence of ADA, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and effectiveness of tarlatamab-dlle is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with tarlatamab-dlle.

No studies have been conducted to evaluate the effects of tarlatamab-dlle on fertility.

14 CLINICAL STUDIES

14.1 Small Cell Lung Cancer

DeLLphi-304

The efficacy of IMDELLTRA was evaluated in DeLLphi-304 (NCT05740566), a multicenter, randomized, open-label trial. Eligible patients were required to have SCLC with disease progression following treatment with platinum-based chemotherapy with or without an anti-PD-(L)1 antibody. Patients were required to have an ECOG Performance Status of 0 or 1 and at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Patients with symptomatic brain metastases or active immunodeficiency were ineligible.

A total of 509 patients were randomized 1:1 to receive either IMDELLTRA (N=254) at an initial dose of 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter until disease progression or unacceptable toxicity or Investigator's choice of standard of care (SOC) chemotherapy (N=255) (topotecan [73%], lurbinectedin [18%] or amrubicin [9%]) until unacceptable toxicity or disease progression. Randomization was stratified by prior anti-PD-(L)1 exposure (yes versus no), platinum sensitivity status (chemotherapy-free interval (CFI) ≥ 180 days, < 180 to ≥ 90 days, or < 90 days), presence (previous or current) of brain metastases (yes versus no) and investigator's choice of standard of care (topotecan/amrubicin versus lurbinectedin).

The median age was 65 years (range: 20 to 86); 52% age 65 or older; 69% male; 57% White, 40% Asian**,** 1.4% were other races or had race not reported, 1% Black or African American, 0.4% American Indian or Alaska Native; 32% had ECOG PS of 0 and 67% ECOG PS of 1; 100% had extensive stage disease at baseline of whom 91% had metastatic disease; 45% had brain metastases at baseline; 35% had liver metastases at baseline. Sixty-nine percent (69%) of patients were former smokers, 21% were current smokers, 11% were never smokers. All patients received prior platinum therapy; 71% received prior anti-PD-(L)1 therapy; 223 patients (44%) had chemotherapy-free interval < 90 days after end of first line platinum therapy, while 286 patients (56%) had chemotherapy-free interval ≥ 90 days.

The major efficacy outcome measure was overall survival (OS). Key secondary efficacy outcome measures included progression-free survival (PFS) based on investigator assessment per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and select patient reported outcomes.

Efficacy results are summarized in Table 18 and Figure 1.

Table 18. Efficacy Results for Patients with SCLC who received IMDELLTRA

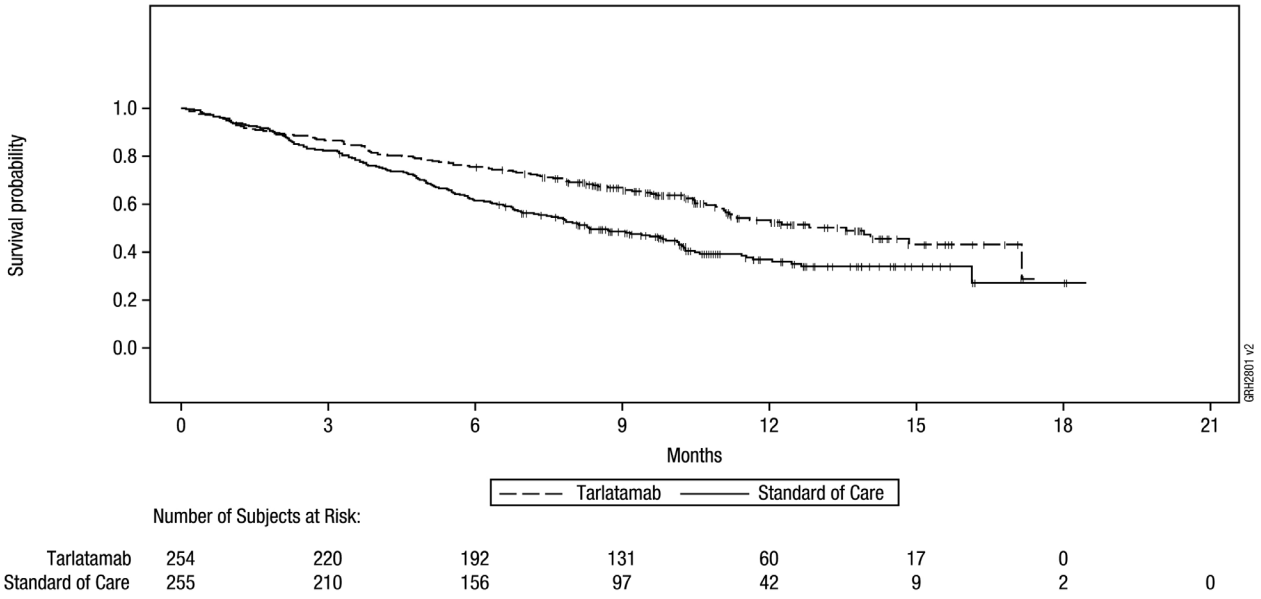
Efficacy Parameter	IMDELLTRA (N = 254)	Standard of Care (N = 255)
Overall Survival (OS)		
Deaths (%)	111 (43.7)	152 (59.6)
Median[a] in months (95% CI)	13.6 (11.1, NE)	8.3 (7.0, 10.2)
Hazard ratio[b] (95% CI)	0.60 (0.47, 0.77)	
p-value[c]	<0.001	

Efficacy Parameter	IMDELLTRA (N = 254)	Standard of Care (N = 255)
Progression-free Survival (PFS)[d]		
Events (%)	191 (75.2)	205 (80.4)
Median[a] in months (95% CI)	4.2 (3.0, 4.4)	3.2 (2.9, 4.2)
Hazard ratio[b] (95% CI)	0.72 (0.59, 0.88)	
p-value[c]	<0.001	

[a] per Kaplan-Meier estimates
[b] Hazard ratio based on the stratified Cox proportional hazard model
[c] p-value based on the stratified log-rank test
[d] PFS based on investigator assessment per RECIST 1.1

In a pre-specified exploratory subgroup analysis, the HR for OS was similar between patients with a chemotherapy-free interval (CFI) <90 days (n=223) and patients with a CFI ≥90 days (n=286), with HRs of 0.60 (95% CI: 0.43, 0.84) and 0.65 (95% CI: 0.45, 0.93), respectively.

Figure 1: Kaplan-Meier Plot of Overall Survival in ITT on DeLLphi-304

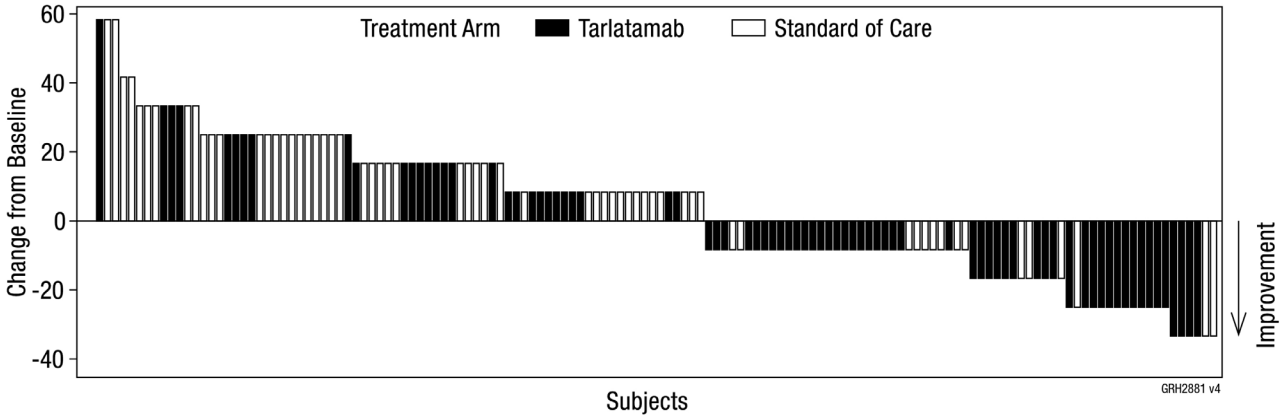


The analysis of mean change from baseline in dyspnea as assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 at week 18 demonstrated a statistically significant improvement in patients randomized to IMDELLTRA compared to SOC. At week 18, 149 patients (59%) randomized to IMDELLTRA and 116 (45%) patients randomized to SOC were still on treatment, and the compliance rates were 79% and 76% respectively at that timepoint.

Figure 2 shows the change from baseline in dyspnea at week 18 in patients who had a change from baseline score at week 18 (n=116 for IMDELLTRA, n=88 for SOC). Two patients with a missing baseline value, both from the IMDELLTRA arm, are not included

in the waterfall plot. Patients with no change in dyspnea score are not graphically represented in Figure 2 (n=38 for IMDELLTRA, n=26 for SOC).

Figure 2: Waterfall plot of Change From Baseline in Dyspnea (Composite Score) at Week 18



DeLLphi-301

The efficacy of IMDELLTRA was evaluated in DeLLphi-301 [NCT05060016], an open-label, multicenter, multi-cohort clinical trial. Eligible patients were required to have relapsed/refractory SCLC with disease progression after receiving previous treatment with platinum-based chemotherapy and at least one other line of prior therapy, an ECOG Performance Status of 0 or 1, and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1). The trial excluded patients with symptomatic brain metastases, evidence of interstitial lung disease or non-infectious pneumonitis, and active immunodeficiency.

A total of 99 patients received IMDELLTRA intravenously at an initial dose of 1 mg on Cycle 1 Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter until disease progression or unacceptable toxicity.

The study population characteristics were: median age 64 years (range: 35 to 82); 48% of patients ≥ 65 years and 10% of patients ≥ 75 years; 72% male; 58% White, 41% Asian; 1% Hispanic or Latino; and 74% have ECOG 1.

Ninety-seven percent of patients had metastatic disease at baseline; 22% had brain metastases at baseline; and 92% were former/current smokers. All patients received prior platinum-based chemotherapy (median two lines); 74% received prior anti-PD-(L)1 therapy (including 59% who received anti-PD[L]1 therapy in combination with platinum-based chemotherapy in the frontline setting); 51% received prior topoisomerase I inhibitor (including 20% who received topotecan). Platinum sensitivity status, defined by time to progression after first line platinum therapy, was known for 69/99 patients. Twenty-seven patients (27%) had platinum-resistant SCLC, defined as time to progression < 90 days after first line platinum therapy, while 42 patients (42%) had platinum-sensitive SCLC.

Tumor assessments were performed every 6 weeks for the first 48 weeks and every 12 weeks thereafter. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) as evaluated by Blinded Independent Central Review (BICR) according to RECIST v1.1.

Efficacy results are presented in Table 19.

Table 19. Efficacy Results for DeLLphi-301

Efficacy Parameter	IMDELLTRA (N = 99)
Overall Response Rate (ORR)	
ORR, % (95% CI)[a]	40 (31, 51)
Complete Response, n (%)	2 (2)
Partial Response, n (%)	38 (38)
Duration of Response (DOR)[a]	
Median[b], months (range)	9.7 (2.7, 20.7+)
Duration ≥ 6 months[c], %	68
Duration ≥ 12 months[c], %	40

[a] Assessed by Blinded Independent Central Review, CI = Confidence Interval
[b] Median based on Kaplan-Meier estimate.
[c] Based on observed duration of response.

Of the 69 patients with available data regarding platinum sensitivity status, the ORR was 52% (95% CI: 32, 71) in 27 patients with platinum-resistant SCLC and 31% (95% CI: 18, 47) in 42 patients with platinum-sensitive SCLC.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

IMDELLTRA (tarlatamab-dlle) for injection is a sterile, preservative-free, white to slightly yellow, lyophilized powder supplied as follows:

- 1 mg package (NDC 55513-059-01) contains 1 single-dose vial of 1 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer.
- 10 mg package (NDC 55513-077-01) contains 1 single-dose vial of 10 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer.

16.2 Storage and Handling

Store IMDELLTRA and IV Solution Stabilizer (IVSS) vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze.

IMDELLTRA and IV Solution Stabilizer (IVSS) vials may be kept at room temperature between 20°C to 25°C (68°F to 77°F) for up to 24 hours in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Cytokine Release Syndrome (CRS)

Inform patients and their caregivers of the risk of CRS, and to immediately contact their healthcare provider for signs and symptoms associated with CRS including pyrexia, hypotension, fatigue, tachycardia, headache, hypoxia, nausea and vomiting *[see Warnings and Precautions (5.1)]*.

Advise patients that they should be monitored from the start of the IMDELLTRA infusion for 22 to 24 hours on Cycle 1 Day 1 and Cycle 1 Day 8 doses in an appropriate healthcare setting *[see Warnings and Precautions (5.1)]*.

Advise patients to remain within 1 hour of an appropriate healthcare setting for a total of 48 hours from start of the infusion with IMDELLTRA following Cycle 1 Day 1 and Cycle 1 Day 8 doses, accompanied by a caregiver.

Neurologic Toxicity Including Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

Discuss the signs and symptoms associated with ICANS with patients and their caregivers. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of ICANS, such as encephalopathy, confusion, delirium, seizure, ataxia, weakness or numbness of arms and legs, tremor, and headache.

Advise patients who experience neurologic toxicity or symptoms of ICANS to refrain from driving, operating heavy or potentially dangerous machinery, and engaging in hazardous occupations or activities during treatment with IMDELLTRA *[see Warnings and Precautions (5.2)]*.

Cytopenias

Discuss the signs and symptoms associated with cytopenias, including neutropenia and febrile neutropenia, anemia, and thrombocytopenia with patients and their caregivers *[see Warnings and Precautions (5.3)]*. Inform patients that they will need to undergo lab tests to monitor blood counts. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of cytopenias.

Infections

Discuss the signs and symptoms of infections with patients and their caregivers. Advise patients of the risk of serious infections, and to immediately contact their healthcare provider for signs or symptoms of infections *[see Warnings and Precautions (5.4)]*.

Hepatotoxicity

Discuss the signs and symptoms of hepatotoxicity and bilirubin with patients and their caregivers. Inform patients that they will need to undergo lab tests to monitor liver function. Advise patients to immediately contact their healthcare provider for signs and symptoms of liver dysfunction *[see Warnings and Precautions (5.5)]*.

Hypersensitivity

Discuss the signs and symptoms of allergic reactions with patients and their caregivers. Advise patients to immediately seek medical attention for any signs and symptoms of severe reactions *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider if they are pregnant or become pregnant. Advise females of reproductive potential to use effective contraception during treatment with IMDELLTRA and for 2 months after the last dose *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with IMDELLTRA and for 2 months after the last dose *[see Use in Specific Populations (8.2)]*.

AMGEN

IMDELLTRA® (tarlatamab-dlle)

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799 U.S.A.
U.S. License No. 1080
Patent: http://pat.amgen.com/imdelltra/

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MEDICATION GUIDE
IMDELLTRA® (im del trah)
(tarlatamab-dlle)
for injection, for intravenous use

What is the most important information I should know about IMDELLTRA?

IMDELLTRA can cause serious side effects, including:

- **Cytokine Release Syndrome (CRS).** CRS is common during treatment with IMDELLTRA and can also be severe, life-threatening, or cause death. Tell your healthcare provider or get medical help right away if you develop any signs or symptoms of CRS, including:
  - fever of 100.4°F (38°C) or higher
  - low blood pressure
  - tiredness
  - fast heartbeat or dizziness
  - headache
  - shortness of breath or trouble breathing
  - nausea and vomiting
  - confusion, restlessness, or feeling anxious
  - problems with balance and movement, such as trouble walking
  - heart, liver, or kidney problems
  - blood clots or unusual bleeding or bleeding that lasts a long time

  Due to the risk of CRS, you will receive IMDELLTRA on a "step-up dosing schedule":
  - The step-up dosing schedule is when you receive a smaller dose of IMDELLTRA on Day 1 of your first treatment cycle (Cycle 1).
  - You will receive the full treatment dose of IMDELLTRA on Day 8 and Day 15 of Cycle 1. You will receive the full treatment dose 1 time every 2 weeks after Day 15 of Cycle 1.
  - If your dose of IMDELLTRA is delayed for any reason, you may need to repeat the step-up dosing schedule.
  - Before receiving your Day 1 and Day 8 doses of Cycle 1 of IMDELLTRA, you will be given a medicine to help reduce your risk of CRS. This will be given into your vein by intravenous (IV) infusion. You will also receive IV fluids after each of your Cycle 1 Day 1 and Day 8 doses. Your healthcare provider will decide if you need to receive medicines to help reduce your risk of CRS with future doses.
  - See **"How will I receive IMDELLTRA?"** for more information about how you will receive IMDELLTRA.
- **Neurologic Problems.** IMDELLTRA can cause neurologic problems that can be severe, life-threatening, or cause death. Neurologic problems may happen days or weeks after you receive IMDELLTRA. Your healthcare provider may refer you to a healthcare provider who specializes in neurologic problems. Tell your healthcare provider right away if you develop any signs or symptoms of neurologic problems, including:
  - changes in taste
  - headache
  - numbness or tingling of your hands or feet
  - dizziness
  - trouble sleeping
  - muscle weakness or numbness of arms or legs
  - problems with walking, or loss of balance or coordination
  - trouble speaking, memory loss, or personality changes
  - confusion, feeling disoriented, slow thinking, or not being able to think clearly
  - fainting or loss of consciousness
  - seizures
  - shaking (tremors)
  - sleepiness
  - feeling like you have no energy

Due to the risk of CRS and neurologic problems you will receive the following monitoring during treatment with IMDELLTRA:

- **For Day 1 and Day 8 of Cycle 1 doses**, your healthcare provider will monitor you **for 22 to 24 hours from the start of the IMDELLTRA infusion in an appropriate healthcare setting** that can manage these side effects.
- **You should remain within 1 hour of an appropriate healthcare setting for a total of 48 hours** from the start of the IMDELLTRA infusion after your Day 1 and Day 8 of Cycle 1 doses **and be accompanied by a caregiver.**
- **For Day 15 of Cycle 1 and Cycle 2 doses**, your healthcare provider will watch you **for 6 to 8 hours** after the IMDELLTRA infusion.
- **For Cycle 3 and Cycle 4 doses**, your healthcare provider will watch you **for 3 to 4 hours** after the IMDELLTRA infusion.
- **For Cycle 5 and later doses**, your healthcare provider will watch you **for 2 hours** after the IMDELLTRA infusion.

Your healthcare provider will monitor you for signs and symptoms of CRS and neurologic problems during treatment with IMDELLTRA and treat you as needed. You may be hospitalized if you develop signs or symptoms of CRS or neurologic problems during treatment with IMDELLTRA. Your healthcare provider may temporarily stop or completely stop your treatment with IMDELLTRA if you develop CRS or neurologic problems.

See **"What are the possible side effects of IMDELLTRA?"** for more information about side effects.

What is IMDELLTRA?

IMDELLTRA is a prescription medicine used to treat adults with extensive stage small cell lung cancer (ES-SCLC), which is cancer that has spread throughout the lung or to other parts of the body, **and**
who have received treatment with chemotherapy that contains platinum, and it did not work or is no longer working.

It is not known if IMDELLTRA is safe and effective in children.

Before receiving IMDELLTRA, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection
- are pregnant or plan to become pregnant. IMDELLTRA may harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with IMDELLTRA.
  - You should use an effective form of birth control (contraception) during treatment with IMDELLTRA, and for 2 months after your last dose of IMDELLTRA.
  - Tell your healthcare provider right away if you become pregnant or think that you may be pregnant during treatment with IMDELLTRA.
- are breastfeeding or plan to breastfeed. It is not known if IMDELLTRA passes into your breast milk. Do not breastfeed during treatment with IMDELLTRA and for 2 months after the last dose of IMDELLTRA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive IMDELLTRA?

- IMDELLTRA will be given to you by your healthcare provider by intravenous (IV) infusion through a needle placed in a vein. The infusion will take about 1 hour.
- Your IMDELLTRA treatment schedule is divided into cycles that are usually 28 days (4 weeks) long.
- Your healthcare provider will decide how many treatment cycles you will receive.
- See **"What is the most important information I should know about IMDELLTRA?"** for more information about how you will receive IMDELLTRA.

What should I avoid while receiving IMDELLTRA?

Do not drive, operate heavy or potentially dangerous machinery or do other dangerous activities, including work-related activities, during treatment with IMDELLTRA if you develop dizziness, confusion, tremors, sleepiness, or any other symptoms that impair consciousness until your signs and symptoms go away. These may be signs and symptoms of neurologic problems. See "**What is the most important information I should know about IMDELLTRA**" for more information about signs and symptoms of neurologic problems.

What are the possible side effects of IMDELLTRA?

IMDELLTRA can cause serious side effects, including:

- See **"What is the most important information I should know about IMDELLTRA?"**
- **Low blood cell counts (cytopenia).** Decreased blood cell counts can be severe and may include the following:
  - low white blood cell counts (neutropenia). Low white blood cells can increase your risk for infection.
  - low red blood cell counts (anemia). Low red blood cells can cause tiredness and shortness of breath.
  - low platelet counts (thrombocytopenia). Low platelet counts can cause bruising or bleeding problems.
- **Infections.** IMDELLTRA can cause serious infections that can be life-threatening and cause death. Your healthcare provider will check you for signs and symptoms of infection before and during treatment with IMDELLTRA. Tell your healthcare provider right away if you develop any signs or symptoms of infection during treatment with IMDELLTRA, including:
  - fever of 100.4°F (38°C) or higher
  - cough
  - chest pain
  - tiredness
  - shortness of breath
  - painful rash
  - sore throat or runny nose
  - pain during urination
  - feeling weak or generally unwell
  - yeast infections in the mouth or other areas
- **Liver problems.** IMDELLTRA can cause increased liver enzymes and bilirubin in your blood. These increases can happen with or without you also having CRS. Tell your healthcare provider right away if you develop any signs or symptoms of liver problems, including:
  - tiredness
  - loss of appetite
  - pain in your right upper stomach-area (abdomen)
  - dark urine
  - yellowing of your skin or the white part of your eyes

- **Allergic reactions.** IMDELLTRA can cause allergic reactions that can be severe. Go to the nearest emergency room or get medical help right away if you develop any signs or symptoms of a severe allergic reaction during treatment with IMDELLTRA, including:
  - shortness of breath or trouble breathing
  - pain or tightness in your chest and back
  - wheezing
  - coughing
  - feeling lightheaded or dizzy
  - rash

Your healthcare provider will do bloodwork before you start and during treatment with IMDELLTRA. Your healthcare provider will monitor you for signs or symptoms of these serious side effects during treatment and may temporarily or completely stop treatment with IMDELLTRA if you develop certain serious side effects.

The most common side effects of IMDELLTRA also include:

- tiredness
- decreased appetite
- a bad or metallic taste in your mouth
- fever
- muscle or bone pain
- constipation
- nausea

The most common severe abnormal blood test results with IMDELLTRA include: decreased white blood cells, decreased sodium, and increased uric acid.

These are not all of the possible side effects of IMDELLTRA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of IMDELLTRA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about IMDELLTRA that is written for health professionals.

What are the ingredients in IMDELLTRA?

Active ingredients: tarlatamab-dlle
Inactive ingredients: glutamic acid, polysorbate 80, sucrose, and sodium hydroxide.
Inactive ingredients of IV Solution Stabilizer: citric acid monohydrate, lysine hydrochloride, polysorbate 80, sodium hydroxide and water for Injection.

Manufactured by: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799
U.S. License No. 1080

For more information, go to www.imdelltra.com or call Amgen at 1-800-772-6436.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 11/2025

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761344Orig1s001

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Supplemental BLA (Efficacy Supplement)
Application Number(s)	BLA 761344/S-001
Priority or Standard	Priority
Submit Date(s)	June 18, 2025
Received Date(s)	June 18, 2025
PDUFA Goal Date	December 18, 2025
Division/Office	Division of Oncology 2/ Office of Oncologic Diseases
Review Completion Date	November 19, 2025
Established Name	Tarlatamab
(Proposed) Trade Name	IMDELLTRA
Pharmacologic Class	Delta-like ligand 3-directed CD3 T-cell engager
Code name	AMG 757
Applicant	Amgen, Inc. (Amgen)
Formulation(s)	Intravenous
Dosing Regimen	An initial dose of 1 mg on Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter
Applicant Proposed Indication(s)/Population(s)	(b) (4) [redacted]
Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	IMDELLTRA is indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy

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OPQA=Office of Product Quality Assessment
OPMA=Office of Pharmaceutical Manufacturing Assessment
RBPM=Regulatory Business Process Manager
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP=Division of Medical Policy Programs

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Glossary

ADA	antidrug antibodies
AE	Adverse event
AMQ	Amgen MedDRA Query
BICR	Blinded independent central review
BLA	biologics license application
BRF	Benefit Risk Framework
BUN	Blood urea nitrogen
BTSR	best tumor size response
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFI	Chemotherapy free interval
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD	Chronic kidney disease
CK-MB	Creatine kinase–myocardial band
CL	Clearance
CoA	Clinical outcome assessment
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CRF	case report form
CRS	cytokine release syndrome
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cutoff

DCR	disease control rate
DLL3	delta-like ligand 3
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOI	Events of interest
ER	Exposure-response
ES-SCLC	Extensive-stage small cell lung cancer
FDA	Food and Drug Administration
GCP	good clinical practice
GLMM	Generalized Linear Mixed Model
GT	Grouped term
HR	Hazard ratio
ICANS	immune effector cell-associated neurotoxicity syndrome
ICH	International Conference on Harmonization
INN	International Nonproprietary Name
IPD	Important protocol deviation
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
KM	Kaplan-meier
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
Mm	Millimeter
MMRM	Mixed Model for Repeated Measures
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NCCN	National Comprehensive Cancer Network

NDA	new drug application
NE	Not estimable
OCE	Oncology Center of Excellence
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	Overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD-1	programmed death protein 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PMR	Post-marketing requirement
PRO	patient reported outcome
Q1	first quartile
Q3	third quartile
Q2W	every 2 weeks
Q3W	every 3 weeks
QLQ-LC13	Quality of Life Questionnaire Lung Cancer 13
QLQ-C30	Quality of Life Questionnaire 30
REMS	risk evaluation and mitigation strategy
REML	restricted maximum likelihood
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
SAP	statistical analysis plan
sBLA	supplemental Biologics License Application
SCLC	small cell lung cancer
SOC	standard of care

TEAE	Treatment-emergent adverse event
US	United States
Vc	central volume of distribution

1 Executive Summary

1.1. Product Introduction

Tarlatamab-dlle (IMDELLTRA; herein referred to as tarlatamab) is a bispecific T-cell engager that binds to delta-like ligand 3 (DLL3) expressed on the surface of cells, including tumor cells, and CD3 expressed on the surface of T-cells. Tarlatamab causes T-cell activation, release of inflammatory cytokines and lysis of DLL3-expressing cells.

Tarlatamab was granted accelerated approval in May 2024 for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy. The recommended dosage for tarlatamab is an initial dose of 1 mg administered as an intravenous infusion over 1 hour on Cycle 1 Day 1, followed by 10 mg on Cycle 1 Day 8 and Day 15 then every 2 weeks thereafter until disease progression or unacceptable toxicity.

The Applicant's proposed indication for this sBLA, intended to support the traditional approval of tarlatamab, is (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The primary trial supporting this supplemental biologics license application (sBLA) for the proposed indication is DeLLphi-304 (Study 20210004), a multicenter, international, open-label, randomized trial in patients with SCLC whose disease had progressed after one prior platinum-containing therapy regimen. A total of 509 patients were randomized 1:1 to receive tarlatamab or investigator's choice of standard of care (SOC) therapy (lurbinectedin, topotecan or amrubicin). Patients received treatment until disease progression, unacceptable toxicity or another criterion for discontinuation was met. The primary endpoint of DeLLphi-304 was overall survival (OS), and key secondary endpoints were progression-free survival (PFS) as assessed by investigator according to RECIST v1.1 and patient reported outcomes (PRO); dyspnea, chest pain, cough, physical functioning and global health status.

At the first prespecified interim analysis of OS, with a data cutoff date of January 29, 2025, when approximately 76% of the expected OS events had occurred, results for both OS and PFS were statistically significant. The hazard ratio (HR) for OS was 0.60 (95% CI: 0.47, 0.77; p <0.001) favoring the tarlatamab arm with a median OS of 13.6 months (95% CI: 11.1, not estimable [NE]) in the tarlatamab arm and 8.3 months (95% CI: 7.0, 10.2) in the SOC arm. The HR for PFS was 0.72 (95% CI: 0.59, 0.88; p<0.001) with a median PFS of 4.2 months (95% CI: 3.0, 4.4) in the tarlatamab arm and 3.2 months (95% CI: 2.9, 4.2) in the SOC arm. Objective response rate (ORR, which may also be referred to as overall response rate in labeling) was 35% (95% CI: 29,

41) in the tarlatamab arm versus 20% (95% CI: 16, 26) in the SOC arm.

DeLLphi-301 (Study 20200491), the trial which supported the accelerated approval of tarlatamab for the treatment of adult patients with ES-SCLC with disease progression on or after platinum-based chemotherapy based on demonstration of an ORR by blinded independent central review (BICR) of 40% (95% CI: 31, 51) with a median DOR of 9.7 months (95% CI: 6.9, NE), provides supportive evidence of effectiveness. Therefore, Substantial Evidence of Effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

The submitted evidence meets the statutory evidentiary standard for traditional approval of tarlatamab for the treatment of adult patients with ES-SCLC with disease progression on or after platinum-based chemotherapy. The observed statistically significant improvement in OS with a HR of 0.60, corresponding to a 5.3-month difference in median OS, is clinically meaningful and represents a major improvement for patients with ES-SCLC. The positive OS results are supported by a statistically significant benefit in PFS, as well as a higher ORR in the tarlatamab arm vs the SOC arm. In addition, the PRO endpoint of mean change from baseline in dyspnea as assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 at week 18 demonstrated a statistically significant improvement in patients randomized to tarlatamab compared to SOC.

Overall, these results provide substantial evidence of effectiveness and support a recommendation for the traditional approval of tarlatamab for the following indication: *treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy*.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Lung cancer is the leading cause of cancer-related mortality in the US and worldwide (Siegel, 2023). Approximately 15% of lung cancers diagnosed are small cell lung cancer (American Cancer Society, 2025). The majority of patients with SCLC have extensive stage SCLC (ES SCLC) at presentation. First-line treatment for ES-SCLC generally consists of etoposide in combination with platinum chemotherapy and a programmed death-ligand 1 (PD-L1) blocking antibody (atezolizumab or durvalumab). Although the response rate to initial treatment is high with ORR of 60-70%, nearly all patients relapse after initial therapy and the median overall survival from front-line ES-SCLC trials is approximately 12 to 13 months (Liu 2021, Paz-Ares 2022). The 5-year survival for ES-SCLC is less than 2% (Basumallik 2023). Depending on the interval between completion of chemotherapy and detection of relapse, treatment options include retreatment with a platinum-based regimen or use of single agent chemotherapy.

Topotecan is the only therapy with traditional approval in the US for patients with SCLC whose disease has progressed after first-line chemotherapy; the approved indication is for chemotherapy-sensitive SCLC, with topotecan demonstrating an ORR of 24% (95% CI: 16%, 32%) with a median duration of response (DOR) of 3.3 months. There is no therapy with traditional approval for patients with platinum-resistant SCLC. Lurbinectedin has received accelerated approval for the treatment of adult patients with metastatic SCLC whose disease has progressed on or after platinum-based chemotherapy based on an ORR as assessed by independent review committee of 30% (95% CI: 22%, 40%) with a median DOR of 5.1 months (95% CI: 4.9, 6.4); ORR was 43% (95% CI: 31%, 57%) in the platinum-sensitive subgroup and 13% (95% CI: 5%, 27%) in the platinum-resistant subgroup. Tarlatamab received accelerated approval for the treatment of adult patients with ES-SCLC with disease progression on or after platinum-based chemotherapy based on the results described in the paragraph below. In addition to topotecan, lurbinectedin and tarlatamab, other therapeutic options that are not FDA approved include taxanes, irinotecan, doxorubicin, gemcitabine, and temozolomide.

Tarlatamab is a bispecific delta-like ligand 3 (DLL3)-directed CD3 T-cell engager. Tarlatamab causes T-cell activation, production of inflammatory cytokines and release of cytotoxic proteins which results in redirected lysis of DLL3-expressing cells. Tarlatamab received accelerated approval on May 16, 2024, for the treatment of patients with ES-SCLC with disease progression on or after platinum-based chemotherapy based on an ORR of 40% (95% CI: 31%, 51%) by BICR with a median DOR of 9.7 months (95% CI: 6.9, NE), in patients with

ES-SCLC whose disease had progressed on prior platinum chemotherapy and one other systemic therapy (in the DeLLphi-301 study).

The primary trial supporting this sBLA is DeLLphi-304, a multicenter, international, open-label, randomized trial in patients with SCLC whose disease had progressed after one prior platinum-containing therapy regimen. A total of 509 patients were randomized 1:1 to receive tarlatamab or investigator's choice of standard of care (SOC) therapy (lurbinectedin, topotecan or amrubicin [lurbinectedin or topotecan in the US, Canada, Australia, Singapore, Korea, amrubicin in Japan and topotecan in all countries except Japan]) until disease progression, unacceptable toxicity or another criterion for discontinuation was met. The primary endpoint of DeLLphi-304 was overall survival (OS), and key secondary endpoints for the trial including progression free survival (PFS) as assessed by investigator according to RECIST v1.1 and patient reported outcomes (PRO; dyspnea, chest pain, cough, physical functioning and global health status.

Of the 509 patients randomized, 71% had received prior anti-PD-(L)1 therapy. At the first prespecified interim analysis of OS, with a data cutoff date of January 29, 2025, when approximately 76% of the expected OS events had occurred, results for both OS and PFS were statistically significant. The hazard ratio (HR) for OS was 0.60 (95% CI: 0.47, 0.77; $p<0.001$) favoring the tarlatamab arm with a median OS of 13.6 months (95% CI: 11.1, not estimable [NE]) in the tarlatamab arm and 8.3 months (95% CI: 7.0, 10.2) in the SOC arm. In a pre-specified exploratory subgroup analysis, the HR for OS was similar between patients with a chemotherapy-free interval (CFI) <90 days (n=223) and patients with a CFI ≥90 days (n=286), with HRs of 0.60 (95% CI: 0.43, 0.84) and 0.65 (95% CI: 0.45, 0.93), respectively. The HR for PFS was 0.72 (95% CI: 0.59, 0.88; $p<0.001$) with a median PFS of 4.2 months (95% CI: 3.0, 4.4) in the tarlatamab arm and 3.2 months (95% CI: 2.9, 4.2) in the SOC arm. ORR was 35% (95% CI: 29, 41) in the tarlatamab arm versus 20% (95% CI: 16, 26) in the SOC arm. In addition, the PRO endpoint of mean change from baseline in dyspnea as assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 at week 18 demonstrated a statistically significant improvement in patients randomized to tarlatamab compared to SOC.

The observed safety profile of tarlatamab is considered acceptable in the context of a life-threatening disease. The safety review for DeLLphi-304 included 496 patients who received at least one dose of therapy in the tarlatamab arm (n=252) or in the SOC arm (n=244). Overall, there were lower rates of treatment-emergent adverse events (TEAEs) leading to discontinuation (6% vs. 13%), treatment interruption (38% vs. 50%) and Grade ≥3 TEAEs (56% vs 80%) in the tarlatamab arm compared to the SOC arm, while the rate of fatal TEAEs (8% vs. 9%) and serious TEAEs (52% vs 52%) were similar between arms. The most common AEs (≥20%) observed with tarlatamab were cytokine release syndrome (CRS; 56%), fatigue (39%), decreased appetite (37%), constipation (30%) pyrexia (29%), dysgeusia (28%), musculoskeletal pain (27%), and nausea (25% each). Serious adverse reactions occurring in >3% of patients who received tarlatamab included CRS (17%), pyrexia (6%), pneumonia (5%) and immune effector cell-associated neurotoxicity syndrome (ICANS; 3.6%). Fatal adverse in patients who received tarlatamab included

one fatal adverse reaction of ICANS (0.4%); fatal adverse reactions occurring in more than one patient included pneumonia (1.6%), cardio-respiratory arrest (1.6%), and sepsis (0.8%).

The key safety concerns for tarlatamab include cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), both of which are included in a boxed warning in the U.S. Prescribing Information (USPI). Other safety concerns warranting inclusion in the Warnings and Precautions section of the USPI include hepatotoxicity, infections, cytopenias, and hypersensitivity. The safety assessment for these toxicities was based on a pooled safety population which included 473 patients from Studies DeLLphi-300, DeLLphi-301 and DeLLphi-304 who received tarlatamab at the dosage indicated in the USPI.

In the pooled safety population, CRS occurred in 57% of patients treated with tarlatamab including 39% Grade 1, 15% Grade 2, 1.7% Grade 3, and 0.2% Grade 4. Among the 268 patients who experienced CRS, 73% had CRS after the first dose, 60% had CRS after the second dose, and 15% had CRS following the third or later dose. The median time to onset of all grade CRS from most recent dose of tarlatamab was 16 hours (range: start of infusion to 15 days). Following the Cycle 1 Day 1, Day 8, Day 15 infusions, 24%, 8%, and 1% of patients, respectively, experienced Grade ≥ 2 CRS. From Cycle 2 onwards, 1.5% of patients experienced Grade ≥ 2 CRS. Of the patients who experienced CRS, 31% received steroids and 10% required tocilizumab.

For this application, (b) (4)

Of the 473 patients from Studies DeLLphi-300, DeLLphi-301 and DeLLphi-304 who received tarlatamab at the dosage indicated in the USPI, 400 (85%) had 24 to 48 hours of monitoring for CRS, while 73 (15%) had 6 to 8 hours of monitoring. The majority of patients who received tarlatamab in DeLLphi-304 had 48 hours of monitoring (n=209, 83%), while only 43 patients (17%) had 6 to 8 hours monitoring (instituted via an amendment to the protocol). (b) (4)

(b) (4)

When reviewing data from patients who had 6 to 8 hour monitoring compared to 24 to 48 hour monitoring, the reported incidence of CRS was slightly lower in the 6 to 8 hour monitoring group (48%) compared with the 24 to 48 hour monitoring group (58%), with low rates of grade ≥3 AEs and AEs leading to delays and discontinuations for both monitoring periods. In addition, the median time to event, time to resolution and proportion of resolved events were similar between each monitoring period. However, only 19% of patients had CRS events with onset within 8 hours from last prior tarlatamab administration and approximately 25% of the time to onset data was missing for patients who had 6 to 8 hour monitoring. Furthermore, an FDA review of tarlatamab postmarketing data initiated by the Division of Pharmacovigliance identified 240 cases of grade ≥2 CRS. While the majority of events were grade 2 (76%), 16% were grade 3, 6% grade 4 and 1.7% grade 5, representing an increased proportion of higher grade events relative to what has been reported in clinical trials. (b) (4)

Neurologic toxicity occurred in 65% of patients in the pooled safety population, including 7% Grade 3 or higher events and one fatal event (0.2%) of ICANS. The most frequent neurologic toxicities were dysgeusia (34%), headache (17%), peripheral neuropathy, dizziness (9% each), and insomnia (8%). ICANS (or signs and symptoms consistent with ICANS) occurred in 10% of patients, including events with the following preferred terms: ICANS (4.7%), muscular weakness (3.2%), cognitive disorder (0.6%), aphasia (0.6%), depressed level of consciousness (0.4%), seizures (0.4%), encephalopathy (0.4%), and leukoencephalopathy (0.2%). There was one fatal reaction of ICANS. Recurrent ICANS occurred in 1.5% of patients. Of the patients who experienced ICANS, most experienced the event following cycle 1 day 1 (2.5% of patients) and cycle 1 day 8 (3.6%). Following Day 1, Day 8, and Day 15 infusions, 1.3%, 1.3% and 0.4% of patients experienced Grade ≥ 2 ICANS, respectively.

The safety profile was generally consistent with that previously described for tarlatamab in ES-SCLC in the approved product labeling. However, there were several fatal cases of CRS reported in the postmarketing setting; in addition, there was a fatal case of ICANS in the DeLLphi-304 trial. The boxed warning included in labeling at the time of the original BLA approval was updated to note that fatal cases of CRS and ICANS can occur in patients receiving tarlatamab. There were no safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of tarlatamab.

The results from the DeLLphi-304 trial meet the statutory evidentiary standard for traditional approval and provide substantial evidence of effectiveness of tarlatamab for the treatment of patients with ES-SCLC with disease progression on or after platinum-based chemotherapy. The

observed statistically significant improvement in OS with a HR of 0.60, corresponding to a 5.3-month difference in median OS, is clinically meaningful and represents a major improvement for patients with ES-SCLC. The positive OS results are supported by a statistically significant benefit in PFS, as well as a higher ORR in the tarlatamab arm vs the SOC arm. In addition, the PRO endpoint of mean change from baseline in dyspnea as assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 at week 18 demonstrated a statistically significant improvement in patients randomized to tarlatamab compared to SOC. The available data supports a conclusion that the clinical benefits of tarlatamab therapy in this patient population outweigh its risks.

The results of DeLLphi-304 support a favorable risk:benefit assessment and meet the statutory evidentiary standard for approval for the following indication:

Tarlatamab (IMDELLTRA), is indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer-related mortality in the US and worldwide. Approximately 15% of lung cancers diagnosed are small cell lung cancer (SCLC). The majority of patients with SCLC have ES-SCLC at presentation. • Current first-line treatment for ES-SCLC is etoposide in combination with platinum chemotherapy and a PD-L1 blocking antibody (atezolizumab or durvalumab) which is associated with a median overall survival of approximately 9-13 months. • Depending on the interval between completion of chemotherapy and detection of progression or recurrence, treatment options prior to the accelerated approval of tarlatamab included retreatment with a platinum-based regimen (for patients with recurrence >6 months from	ES-SCLC is a serious and life-threatening disease associated with poor survival.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	last dose of platinum) or use of single-agent chemotherapy.	
Current Treatment Options	• In the second-line setting, topotecan is the only therapy with traditional FDA approval for patients with chemotherapy-sensitive SCLC whose disease has progressed following first-line chemotherapy; in patients with SCLC with disease progression occurring ≥60 days of first-line chemotherapy, ORR was 24% (95% CI: 16%, 32%) with a median duration of response of 3.3 months. • While there is no therapy with tradiational approval for platinum-resistant SCLC, based on data from single arm studies using the more standard cut-off of ≥90 days for platinum-sensitive vs. platinum-resistant, reported response rates ranged from 11-31% for patients with platinum-sensitive disease and 2- 7% in patients with platinum-resistant disease. • Lurbinectedin has received accelerated approval for the treatment of adult patients with metastatic SCLC whose disease has progressed on or after platinum-based chemotherapy, with an ORR of 30% (95% CI: 22%, 40%) and a median DOR of 5.1 months (95% CI: 4.9, 6.4). ORR was 43% (95% CI: 31%, 57%) in the platinum-sensitive subgroup and 13% (95% CI: 5%, 27%) in the platinum-resistant subgroup. • Other therapeutic options that are not FDA approved include taxanes, irinotecan, doxorubicin, gemcitabine, and temozolomide	There is an unmet need for the treatment of patients with ES-SCLC with progression after prior platinum-containing therapy. This unmet need is even more profound for patients with platinum-resistant disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Tarlatamab has received accelerated approval for the treatment of patients with ES-SCLC with disease progression on or after platinum-based chemotherapy. In patients who had received prior platinum-based chemotherapy (and at least one other line of systemic therapy), ORR was 40% (95% CI: 31%, 51%) with a median DOR of 9.7 months (95% CI: 6.9, not estimable [NE]), by blinded independent central review. • The primary trial supporting this sBLA is DeLLphi-304, a multicenter, international, open-label, randomized trial, which included 509 patients with ES-SCLC whose disease had progressed after one prior platinum-containing therapy regimen randomized to receive tarlatamab or investigator's choice standard of care (SOC; topotecan, lurbinectedin, or amrubicin) . The primary endpoint of DeLLphi-304 was OS, and a key secondary endpoints were PFS as assessed by investigator per RECIST v1.1 and patient-reported outcomes (PRO; dyspnea, chest pain, cough, physical functioning, and global health status). • DeLLphi-304 demonstrated statistically significant improvements in OS and PFS at the first pre-specified OS interim analysis. The OS HR was 0.60 (95% CI: 0.47, 0.77; p-value <0.001) favoring the tarlatamab	The observed magnitude of improvement in OS is statistically significant and clinically meaningful; the observed improvement in OS with a HR of 0.60, corresponding to a 5.3-month difference in median OS, represents a major improvement for patients with ES-SCLC. The positive OS results are supported by a statistically significant benefit in PFS, as well as a higher ORR in the tarlatamab arm vs the SOC arm. In addition, the PRO endpoint of mean change from baseline in dyspnea as assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 at week 18 demonstrated a statistically significant improvement in patients randomized to tarlatamab compared to SOC. The information in this sBLA provides substantial evidence of effectiveness and meets the statutory evidentiary standard for traditional approval of tarlatamab for the treatment of adult patients with ES-SCLC with disease

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	arm, corresponding to a median OS of 13.6 months (95% CI: 11.1, NE) in the tarlatamab arm and 8.3 months (95% CI: 7, 10.2) in the SOC arm. In a pre-specified exploratory subgroup analysis, the HR for OS was similar between patients with a chemotherapy-free interval (CFI) <90 days (n=223) and patients with a CFI ≥90 days (n=286), with HRs of 0.60 (95% CI: 0.43, 0.84) and 0.65 (95% CI: 0.45, 0.93), respectively. • The PFS HR was 0.72 (95% CI: 0.59, 0.88; p-value <0.001), corresponding to a median PFS of 4.2 months (95% CI: 3, 4.4) in the tarlatamab arm and 3.2 months (95% CI: 2.9, 4.2) in the SOC arm. ORR was 35% (95% CI: 29, 41) in the tarlatamab arm versus 20% (95% CI: 16, 26) in the SOC arm. In addition, the PRO endpoint of mean change from baseline in dyspnea as assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 at week 18 demonstrated a statistically significant improvement in patients randomized to tarlatamab compared to SOC.	progression on or after platinum-based chemotherapy.
Risk and Risk Management	• The primary safety population from DeLLphi-304 includes 496 patients who received at least one dose of therapy in the tarlatamab arm (n=252) and in the SOC arm (n=244). • Overall, there were lower rates of treatment-emergent adverse events (TEAEs) leading to discontinuation (6% vs. 13%) and treatment interruption (38% vs. 50%) and Grade ≥3 TEAEs (56% vs 80%), while the rate of fatal TEAEs (8% vs. 9%), and serious TEAEs (52% vs	The observed safety profile is considered acceptable when assessed in the context of the treatment of a life-threatening disease. (b) (4)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	52%) were similar between arms. • The most common AEs (≥20%) observed with tarlatamab in DeLLphi-304 were cytokine release syndrome (CRS; 56%), fatigue (39%), decreased appetite (37%), constipation (30%), pyrexia (29%), dysgeusia (28%), musculoskeletal pain (27%), and nausea (25%). • Serious adverse reactions occurring in >3% of patients who received tarlatamab included CRS (17%), pyrexia (6%), pneumonia (5%) and immune effector cell-associated neurotoxicity syndrome (ICANS; 3.6%). Fatal adverse in patients who received tarlatamab included one fatal adverse reaction of ICANS (0.4%); fatal adverse reactions occurring in more than one patient included pneumonia (1.6%), cardio-respiratory arrest (1.6%), and sepsis (0.8%). • Key safety concerns for tarlatamab include CRS and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), both of which are included in a boxed warning in the U.S. Prescribing Information (USPI). Other safety concerns warranting inclusion in the Warnings and Precautions section of the USPI include hepatotoxicity, infections, cytopenias, and hypersensitivity. The safety assessment for these toxicities was based on a pooled safety population which included 473 patients from Studies DeLLphi-300, DeLLphi-301 and DeLLphi-304 who received tarlatamab at the dosage indicated in the USPI. • (b) (4)	(b) (4) The safety profile of tarlatamab was generally consistent with that previously described for tarlatamab in ES-SCLC in the approved product labeling. However, given fatal cases of CRS reported in the postmarketing setting and a fatal case of ICANS in the DeLLphi-304 trial, the boxed warning included in labeling at the time of the original BLA approval was updated to note that fatal cases of CRS and ICANS can occur in patients receiving tarlatamab. No new safety concerns required risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of tarlatamab for the proposed indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(b) (4) • There was a fatal adverse event of ICANS in the DeLLphi-304 trial and fatal events of CRS have been reported in the post-marketing setting.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
X	Clinical outcome assessment (COA) data, such as	Section 8.1.2: Study results
X	Patient reported outcome (PRO)	
□	Observer reported outcome (ObsRO)	
□	Clinician reported outcome (ClinRO)	
□	Performance outcome (PerfO)	
□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	

- ☐ Patient-focused drug development or other stakeholder meeting summary reports [e.g., Section 2.1 Analysis of Condition]
- ☐ Observational survey studies designed to capture patient experience data
- ☐ Natural history studies
- ☐ Patient preference studies (e.g., submitted studies or scientific publications)
- ☐ Other: (Please specify)

☐ Patient experience data that was not submitted in the application, but was considered in this review.

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Globally, lung cancer is the most commonly diagnosed cancer and leading cause of cancer death, representing approximately 1 in 8 (12.4%) cancers diagnosed and 1 in 5 (18.7%) cancer deaths (Bray et al, 2024). Small cell lung cancer (SCLC) accounts for ~10% to 15% of lung cancer cases, with an estimated 248,000 to 372,000 new SCLC cases globally in 2022, based on lung cancer incidence estimates (American Cancer Society, 2024; Rudin et al 2021). In the United States (US) there were an estimated 23,500 to 35,000 new SCLC cases in 2024, based on lung cancer incidence estimates (American Cancer Society 2024; Rudin et al 2021; Siegel et al 2024). The disease is highly aggressive, with rapid progression leading to a 5-year survival rate of less than 10% and remains the most lethal lung cancer subtype (Cittolin-Santos et al, 2024).

Small cell lung cancer is a high-grade neuroendocrine tumor marked by an exceptionally high proliferative rate, strong predilection for early metastasis, and poor prognosis (Rudin et al, 2021). While 30% of patients present with disease that can be encompassed by 1 radiotherapy field (limited stage), the majority of cases have disease diagnosed as extensive stage. Although 20% to 30% of patients with limited stage can be cured with radio-chemotherapy, treatment is rarely curative in extensive stage, with over half of patients relapsed within 6 months after first-line chemo-immunotherapy (Cheng et al, 2025; Cheng et al, 2024; Cheng et al, 2022; Wang et al, 2022; Paz-Ares et al, 2019; Horn et al, 2018).

The FDA's Assessment:

FDA agrees with the Applicant's position.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Current first-line treatment of SCLC generally consists of etoposide in combination with either cisplatin or carboplatin. For limited-stage SCLC, this regimen is combined with radiation therapy, while for extensive-stage SCLC, it is combined with a programmed death ligand 1 (PD-L1) immune checkpoint inhibitor—either atezolizumab or durvalumab (National Comprehensive Cancer Network [NCCN] SCLC Guidelines, 2025; Guidelines for Diagnosis and Treatment of Lung Cancer in Japan, 2021; Rudin et al, 2021; Dingemans et al, 2021; Ganti et al, 2021).

Although the first-line regimen in SCLC has a relatively high response rate (80% to 90% for limited stage and 60% to 70% for extensive stage), resistance and relapse almost always occur, usually within the first year after treatment for over half of patients with limited-stage and nearly all patients with extensive-stage SCLC (Petty and Paz-Ares. 2023; Rudin et al, 2021; Yoon et al, 2019; Chan and Coward, 2013). Median overall survival (OS) is approximately 30 months for limited-stage SCLC and 12 to 13 months for extensive-stage SCLC (Schlick et al, 2022; Tariq et al, 2021; Paz-Ares et al, 2019; Horn et al, 2018).

Treatment options for patients with relapsed SCLC are limited, and with currently available therapy, prognosis remains poor. In addition to consideration of platinum rechallenge or clinical trial participation, other recommended regimens in the relapsed or refractory setting include topotecan (Eckardt et al, 2007; O'Brien et al, 2006; von Pawel et al, 1999), lurbinectedin (Trigo et al, 2020), amrubicin in Japan, other chemotherapy agents (eg, cyclophosphamide/doxorubicin/vincristine, docetaxel, etoposide, gemcitabine, temozolomide), or immunotherapy agents (eg, nivolumab, pembrolizumab).

The NCCN guidelines include several therapies as recommended regimens for patients who progress following initial systemic therapy. Among these, topotecan is Food and Drug Administration (FDA)-approved for use in patients with SCLC platinum-sensitive disease who progress at least 60 days after initiation of first-line chemotherapy (NCCN, 2025) (Table 1), while lurbinectedin has received accelerated FDA approval for patients with metastatic SCLC who experience disease progression on or after platinum-based chemotherapy, irrespective of the chemotherapy-free interval.

National Comprehensive Cancer Network guidelines also include lurbinectedin as a recommended regimen in patients who progress subsequent to initial systemic therapy with platinum-based chemotherapy (NCCN, 2025). Lurbinectedin received accelerated approval in August 2020 in the US based on an objective response rate (ORR) (95% CI) as assessed by investigator of 35% (26%, 45%) and median (95% CI) duration of response (DOR) of 5.3 (4.1, 6.4) months (Zepzelca[â] US Prescribing Information, 2023). It is important to note that all subjects enrolled in this study had progressed on or after platinum-based chemotherapy, with only 8% of subjects also having prior immunotherapy. Lurbinectedin is not approved in the EU.

Recent novel therapeutic strategies such as immunotherapy with programmed death protein 1 (PD-1) checkpoint inhibitors have not improved outcomes compared with topotecan in the second-line or later setting (Das et al, 2021; Giffin et al, 2021; Trigo et al, 2020) and the need for durable responses remains high. Additionally, the benefits of immunotherapy in first-line treatment of extensive-stage SCLC are relatively modest (approximately 2 to 3 month increase in median OS) (Paz-Ares et al, 2019; Horn et al, 2018).

A recent large real-world study using a nationwide de-identified electronic health record database in the US found a median overall survival of 4.8 months (95% CI: 4.2-4.9) for patients

with SCLC initiating second-line systemic therapy (Shaw et al, 2024); this aligns with survival rates reported in previous real-world studies of second-line systemic treatment from 2011-2021 (median OS of 4.2 to 7.0 months) (O'Sullivan et al, 2021; Rojo et al, 2020; Schwartzberg et al, 2018; Imai et al, 2017; Garassino et al, 2011).

Median (95% CI) real-world OS from the initiation of second-line therapy was 5.6 (4.9 to 6.3) months among those treated with an anti-PD-L1 agent and 4.5 (4.2 to 4.9) months among those not treated with an anti-PD-L1 agent in the front-line setting.

Overall, the results from trials and real-world evidence studies show that patients with advanced SCLC have poor treatment outcomes with existing therapies in second-line, including those who received first-line anti-PD-L1 therapy, consistent with current standard of care, as well as those treated with platinum rechallenge. Hence, disease burden is high irrespective of prior treatment exposure and the type of regimen used in second line.

In addition to poor survival outcomes associated with relapsed SCLC, patients also face significant challenges in managing cancer-related symptoms, including cough, dyspnea, chest pain, and hemoptysis (Bebb et al, 2023). These symptoms, which are frequently debilitating, substantially impair patients' physical functioning and ability to perform basic activities of daily living (Bennett et al, 2017). Therefore, there remains a significant unmet medical need in patients with advanced SCLC for novel therapies that can support longer survival and reduce disease-associated symptoms with an acceptable safety profile. Tarlatamab is being developed with the goal of addressing this unmet need.

Table 1. Applicant – Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Admin-istration	Efficacy Information	Important Safety and Tolerability Issues	Other comments
FDA Approved Treatments						
Lurbinectin (Zepzelca)	Treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy	2020 Accelerated Approval	3.2 mg/m^2 IV over 1 hour every 21 days	Primary Endpoint - Investigator-assessed ORR: 35% (95% CI: 26, 45) Secondary Endpoints – mDOR: 5.3 months (95% CI: 4.1, 6.4) m mPFS: 3.5 months (95% CI: 2.63, 4.34) mOS: 9.3 mo (95% CI: 6.3, 11.8)	Myelosuppression, hepatotoxicity, extravasation resulting in tissue necrosis, rhabdomyolysis, and embryo-fetal toxicity	The FDA review teams recommended accelerated approval of lurbinectedin for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. This was supported by results from PM1183-B-005-15 (Study B-005), an ongoing, multicenter, open-label, non-randomized, multi-cohort trial evaluating the safety and efficacy of lurbinectedin as a single-agent in adult patients with advanced solid tumors. The efficacy is primarily based on results from a cohort of 105 patients with metastatic SCLC who had disease progression on or after first-line treatment with platinum-based chemotherapy. All patients had received prior platinum-based therapy and 8% had received prior immunotherapy.
Topotecan (Hycamtin) oral capsules	Treatment of patients with relapsed SCLC	2007 (SCLC) Full Approval	2.3 mg/m^2 /day QD for 5 consec- utive days repeated every 21 days	mOS: 6.0 months; HR: 0.64 (95% CI: 0.45, 0.90)	Diarrhea, interstitial lung disease and embryo-fetal toxicity	Randomized, open-label study comparing oral topotecan with best supportive care (BSC) to BSC alone in patients with relapsed SCLC who were prior responders to first-line chemotherapy.

Footnotes on the last page

Table 1. Applicant – Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Administra-tion	Efficacy Information	Important Safety and Tolerability Issues	Other comments
Topotecan (Hycamtin)	Treatment of patients with platinum-sensitive disease who progressed at least 60 days after initiation of first-line chemotherapy	1998 Full Approval	1.5 mg/m^2 IV infusion over 30 min daily on days 1 to 5 of each 21-day cycle until disease progression.	ORR: 24% mDOR: 3.3 mo mOS: 5.8 months Hazard ratio (95% CI): 1.04 (0.78, 1.39) The results of the trial did not show statistically significant improvements in response rate, response duration, time to progression, or OS	Interstitial lung disease, extravasation and tissue injury, and embryo-fetal toxicity. Box Warning: HYCAMTIN can cause severe myelosuppression. Administer first cycle only to patients with baseline neutrophil counts greater than or equal to 1,500/mm^3 and platelet counts greater than or equal to 100,000/mm^3. Monitor blood cell counts on all patients receiving topotecan.	Randomized, open-label study comparing topotecan and cyclophosphamide, doxorubicin (adriamycin), and vincristine (CAV) in patients with limited or extensive-stage SCLC who progressed at least 60 days after completion of first-line chemotherapy. Three open-label, single-arm studies in patients with recurrent or progressive SCLC after treatment with first-line chemotherapy. Study populations included patients with platinum-sensitive SCLC (responders who subsequently progressed ≥ 90 days after completion of first-line therapy) and platinum refractory SCLC (no response to first-line chemotherapy or response followed by progression within 90 days of completing first-line therapy).

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BSC = best supportive care; CAV = cyclophosphamide, doxorubicin (adriamycin), and vincristine; FDA = Food And Drug Administration; HR = hazard ratio; IV = intravenous; mDOR = median duration of response; mPFS = median progression-free survival; mOS = median overall survival; ORR = objective response rate; OS = overall survival; QD = once daily; SCLC = small cell lung cancer; SCLC = small cell lung cancer

The FDA's Assessment:

FDA generally agrees with the Applicant's presentation of current treatment options. Cytotoxic chemotherapies are expected to have differential tumor response based on a patient's "sensitivity" to platinum-based chemotherapy and given this, efficacy is usually assessed separately in subgroups of patients with platinum-sensitive or platinum-resistant disease, with the former group generally being defined as patients who have had disease progression ≥ 90 days after completion of first-line platinum-based chemotherapy and the latter group being defined as patients who have progression < 90 days after completion of first-line platinum-based chemotherapy. Based on data from single arm studies with topotecan using the more standard cut-off of ≥90 days for platinum-sensitive vs. platinum-resistant, reported response rates ranged from 11-31% for patients with platinum-sensitive disease and 2-7% in patients with platinum-resistant disease. For lurbinectedin, which is currently under accelerated approval for the treatment of metastatic SCLC following progression on platinum-based chemotherapy, ORR was 43% (95% CI: 31%, 57%) in the platinum-sensitive subgroup and 13% (95% CI: 5%, 27%) in the platinum-resistant subgroup.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Tarlatamab (International Nonproprietary Name [INN]; AMG 757) was approved in the US under Accelerated Approval on 16 May 2024 for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy. As of 29 May 2025, tarlatamab is approved in 10 countries for the treatment of adult patients with extensive-stage SCLC with disease progression on or after at least 1 or 2 prior lines of therapy, including platinum-based chemotherapy, depending on the country.

The FDA's Assessment:

FDA agrees with the Applicant's position. Tarlatamab was granted accelerated approval based on an ORR of 40% (95% CI: 31%, 51%) in 99 patients who had received prior platinum-based chemotherapy and one other systemic therapy. ORR was 52% (95% CI: 32%, 71%) in patients with platinum-resistant disease and 31% (95% CI: 18%, 47%) in patients with platinum-sensitive disease.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of key interactions with the FDA regarding tarlatamab for the proposed indication, the subject of this marketing application, is provided in Table 2.

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Table 2. Applicant - Summary of Key Interactions With FDA for the Tarlatamab Clinical Program in SCLC

Date	Type and Purpose of Interaction
14 September 2020	Type B end-of-phase 1 meeting for the tarlatamab clinical development program – Clinical
02 September 2021	Type C meeting to discuss designs of the pivotal phase 2 Study 20200491 and the confirmatory phase 3 Study 20210004 – Clinical
05 December 2022	Type B (pre-phase 3) meeting for confirmatory Study 20210004 – Clinical
06 February 2023	Type C Structure and Format Meeting for the planned BLA – Clinical
21 July 2023	Type B pre-BLA Meeting to discuss CMC package for planned BLA – CMC
08 September 2023	Type B pre-BLA Meeting to discuss nonclinical and clinical package for planned BLA – Nonclinical and Clinical
November 2023	In Information Request, Agency agreed to 1-2 hours safety monitoring for Study 20210004 (PA2) with additional safety measures. Due to operational challenges with ongoing study, Amgen aligned with Agency on 6-8 hours monitoring on cycle 1 days 1 and 8 without additional Agency-requested safety measures (PA3)
16 May 2024	Tarlatamab received accelerated approval with postmarketing requirement to complete and submit the results of confirmatory Study 20210004 (tarlatamab vs standard of care) to verify the clinical benefit of tarlatamab.
24 September 2024	Type C Written Response on structure and format of the planned supplemental BLA to include results of confirmatory Study 20210004.
16 May 2025	Type B Pre-sBLA Meeting to discuss data from Study 20210004 and the clinical package for planned sBLA

BLA = biologics license application; CHMP = Committee for Medicinal Products for Human Use; CMC = Chemistry Manufacturing and Controls; EMA = European Medicines Agency; PA = protocol amendment; FDA = Food and Drug Administration; sBLA = supplemental Biologics License Application; SCLC = small cell lung cancer

The FDA's Assessment:

FDA agrees with the Applicant's characterizations of key regulatory milestones.

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical data from Study 20210004 (DeLLphi-304) were submitted to the Agency in support of supplemental Biologics License Application (BLA) 761344/S01 to fulfill Post-Market Requirement (PMR) 4635-2 and to support the conversion of tarlatamab from accelerated approval to regular approval (b) (4) The Applicant, Amgen Inc., was inspected.

The inspection of Amgen was conducted due to deficiencies identified at several clinical sites including one in South Korea (Site #57002) during the original BLA review cycle which included eligibility violations and underreporting of adverse events in the majority of enrolled patients. Based on these deficiencies and the current supplement, FDA issued an information request on July 15, 2025, requiring 100% source data verification at specified sites for Study DeLLphi-304. Amgen responded on July 28, 2025, asserting that comprehensive data verification activities had been performed at all study sites prior to the Primary Analysis.

The Applicant inspection did not reveal significant concerns regarding study conduct, data integrity, Good Clinical Practice (GCP), or regulatory compliance. The inspection verified that Amgen had implemented enhanced data oversight measures as outlined in their information request response. Amgen's oversight of Study DeLLphi-304 appears adequate. Based on this inspection, Study DeLLphi-304 appears to have been conducted adequately, with the data submitted by the Applicant appearing acceptable in support of the proposed indication.

4.2. Product Quality

No product quality data were submitted in these supplemental applications. Refer to CDER/OPQ's product quality review for tarlatamab original submission (BLA 761344).

4.3. Clinical Microbiology

No clinical microbiology data were submitted in these supplemental applications. Refer to CDER's quality microbiology review for tarlatamab original submission (BLA 761344).

4.4. Devices and Companion Diagnostic Issues

The proposed indication for tarlabamab is not limited to a biomarker-selected population; therefore, there was no device or companion diagnostic test reviewed as part of this application.

APPEARS THIS WAY ON ORIGINAL

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

5 Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology data are provided in the current sBLA.

The FDA's Assessment:

FDA agrees.

X	X
Primary Reviewer	Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant submitted an efficacy supplement to support traditional approval of tarlatamab (b) (4)

The proposed recommended dosage is 1 mg on cycle 1 day 1, followed by 10 mg on cycle 1 days 8 and 15, and every 2 weeks thereafter, all administered as 1-hour intravenous infusion. The step-up dosing schedule is designed to mitigate cytokine release syndrome risk.

The key review issue focused on the appropriateness of the proposed dosing regimen in relapsed SCLC, which is considered acceptable based on efficacy and safety data from Studies 20160323, 20200491, and 20210004, as well as the following information:

- The population pharmacokinetic model adequately describes the observed concentration data in the SCLC population.
- The exposure-response analyses support the proposed recommended dosage, demonstrating near-plateau effect for efficacy and relatively flat trend for safety across exposures at this dosage.
- No clinically meaningful covariates were identified that would require dosage modifications.

The incidence of treatment-emergent antidrug antibodies at the 10 mg Q2W regimen was 7.7% (36/445 participants) across pooled studies, with neutralizing antibody incidence of 38% (11/29 participants), which is consistent with previously reported. The labeling was updated with immunogenicity data from Study 20210004 (DeLLphi-304) pooled with the previous two studies (20160323, and 20200491). The presence of antidrug antibodies resulted in approximately 14% higher clearance but did not have a clinically meaningful impact on efficacy or safety as demonstrated by subgroup analyses across ADA-positive and ADA-negative participants. Because of the low occurrence of ADA across these trials, labeling states that the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and effectiveness of tarlatamab is unknown.

Recommendations: The Office of Clinical Pharmacology has reviewed the information contained in BLA761344/S-001. The supplement is approvable from a clinical pharmacology perspective with labeling language agreed upon.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Tarlatamab exhibited approximate dose-proportional increases in exposures in the evaluated dose range of 0.003 mg to 100 mg intravenous (IV) administered every 2 weeks (Q2W) and 200 mg every 3 weeks (Q3W). Following the clinical regimen of 1 mg on day 1, then 10 mg on day 8, day 15, and Q2W thereafter, steady state in tarlatamab serum concentrations were approximately achieved by cycle 2 day 15. Tarlatamab mean C_{trough} values at steady state (cycle 2 day 15 predose) and peak serum concentrations at steady state (cycle 2 day 15, end of infusion) were 0.429 μg/mL and 3.83 μg/mL, based on pooled data across phase 1, phase 2, and phase 3 studies. There was no indication of time-dependent kinetics.

Based on cross-study population pharmacokinetics (PK) analyses, population mean (%CV) for clearance (CL) is estimated to be 0.728 L/day (34%). Vss mean (%CV), based on individual parameters, is estimated to be 8.53 L (33%) and terminal half-life mean (%CV) is estimated to be 10.6 days (31%)

At the clinical regimen of 10 mg Q2W, treatment emergent antidrug antibodies (ADA) incidence was 8.5% (20/234) for Study 20210004, 5.6% (7/125) for the Study 20200491, and 8.2% (7/85) for Study 20160323. An analysis of pooled data from all subjects receiving the 10 mg target dose across Studies 20210004, 20200491, and 20160323 showed that 34 of 444 subjects (7.7%) had developed antitarlatamab binding antibodies. In the phase 2 and phase 3 studies which employed the neutralizing antibodies assay, the neutralizing antibodies incidence was 3.1% (11/359 subjects).

The Applicant's Position:

Across Studies 20160323, 20200491 and 20210004, tarlatamab exhibited approximate dose-proportional increases in exposures in the evaluated dose range. The steady state in tarlatamab serum concentrations were approximately achieved by the start of cycle 2. The model estimated mean (%CV) estimated terminal phase elimination half-life at steady state was 10.6 (31%) days, across the evaluated dose range. The incidence of antitarlatamab antibody development was low. There was no meaningful clinical impact of antitarlatamab antibody development on PK, efficacy or safety.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the clinical pharmacology characterization of tarlatamab. Consistent with the original application which included Studies 20160323 and

20200491, PK parameters with inclusion of Study 20210004 have small numerical changes (refer to Table 3 and section 19.4.1), and values were updated in the labeling.

Table 3. Typical Pharmacokinetic Parameter Values of Tarlatamab Following the Currently Approved Recommended Dosing Regimen of 1 mg D1, 10 mg on D8, D15 and Q2W Thereafter.

	Cavg (ng/mL)	Cmax (ng/mL)	Ctrough (ng/mL)
First step up dose 1mg	106 (26%)	314 (35%)	49 (35%)
First treatment dose 10mg	1,100 (26%)	3,190 (35%)	517 (36%)
Steady state 10mg every 2 weeks	1,040 (37%)	3,640 (35%)	472 (62%)

Source: PopPK report Table 10.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The totality of data from the dose exploration and expansion parts of Study 20160323 supported the selection of 2 target dose levels of 10 and 100 mg Q2W to be further characterized in Study 20200491.

Within the evaluated target dose range, a numerical benefit associated with 10 mg Q2W exposures relative to lower target doses of 3 mg or 1 mg administered as a Q2W regimen was observed. The analysis also displayed numerical benefit in disease control rate (DCR) with exposures associated with 100 mg Q2W regimen, relative to 10 mg Q2W regimen, and therefore supported the selection of 100 mg as the higher dose level (in addition to 10 mg) to be evaluated in Study 20200491.

From a safety and tolerability perspective, a maximal tolerated dose level was not achieved in Study 20160323, within the evaluated target dose range of 0.003 to 100 mg administered as Q2W (or 200 mg Q3W). In summary, these analyses, in addition to the overall manageable safety and tolerability profile of tarlatamab, supported the selection of 10 and 100 mg Q2W target doses to be further evaluated in Part 1 of Study 20200491.

Of the 2 target dose levels assessed in Part 1 of Study 20200491, 10 mg Q2W regimen was selected for further evaluation in Part 2 and Part 3 as well as all subsequent studies utilizing a Q2W regimen.

Part 1 of the Study 20200491 was designed to evaluate the safety and efficacy of 10 and 100 mg doses of tarlatamab. A prespecified interim analysis was conducted to select 1 of the 2 doses for further evaluation after 30 subjects per arm were enrolled and had received at least 1 dose of tarlatamab and had the opportunity to confirm objective response after the first post-treatment scan (or had up to 13 weeks of follow-up). Based on the pre-specified IA in part 1, following confirmation with the agency, the regimen using a 10 mg target dose every 2 weeks (Q2W) with a 1 mg step-dose was selected as the recommended phase 2 dose regimen (RP2D) for IV administration in monotherapy for commercial use and the subsequent studies.

At the time of interim analysis (data cutoff of 27 June 2023), a total of 127 subjects had enrolled in Part 1 of Study 20200491. Of these, 125 subjects received at least 1 dose of tarlatamab and were included in the Safety Analysis Set, and 63 subjects met the criteria for inclusion in the Interim Efficacy Analysis Set. Briefly, measures of efficacy response were similar between the 10 mg and 100 mg groups. In the 10 mg group, the confirmed ORR (assessed by the Investigator) was 34.4% (95% CI: 18.6, 53.2), and the DCR was 75.0% (95% CI: 56.6, 88.5). In the 100 mg group, the confirmed ORR was 35.5% (95% CI: 19.2, 54.6), and the DCR was 64.5% (95% CI: 45.4, 80.8). Compared with the 100 mg group, subjects in the 10 mg group experienced fewer treatment-emergent adverse events leading to discontinuation of tarlatamab, fewer serious adverse events, and fewer fatal adverse events. Consistent with the dose-response data, exposures with the 10 mg target dose regimen were associated with improved tolerability but comparable efficacy relative to the 100 mg dose.

Data from the pivotal study (20210004) confirms the selection of 10 mg Q2W as the optimal dose with regards to safety and efficacy.

The Applicant's Position:

Overall, results of the pooled exposure-response analysis across studies 20160323, 20200491 and 20210004 confirmed that the clinical regimen of 10 mg Q2W reached an efficacy plateau with a manageable safety profile.

The FDA's Assessment:

FDA agrees that the proposed dosage is appropriate for the intended patient population. The selection for the step-up and target dose was reviewed and agreed upon in the review of the original BLA submission (refer to multi-desciplinary review of BLA 761344). The efficacy and safety data from the pivotal trial, Study 20210004, confirmed the selection of 10 mg Q2W which was also supported by the exposure-response analyses that showed that exposures associated

with the 10 mg Q2W regimen reached an efficacy plateau with relatively flat trend for safety across exposures at this dosage.

6.2.2.2. Therapeutic Individualization

Data:

The influence of demographic and subject specific characteristics on the PK of tarlatamab were investigated using population PK. Various demographic variables were evaluated in the covariate testing within the population PK analyses framework. Key demographic factors (age, sex, ethnicity), estimates of renal function, Eastern Cooperative Oncology Group (ECOG) status, did not affect tarlatamab PK.

Like other biologics, body weight was found to be correlated with tarlatamab CL, with increase in body weight associated with increase in CL. However, at the clinical regimen of 1 mg on day 1 followed by 10 mg on day 8, day 15, and Q2W thereafter, body weight is not expected to have a clinically relevant impact on tarlatamab efficacy as the point estimate for the difference between high or low body weight subjects relative to a median bodyweight subject of 72.6 kg is estimated to be within the default boundary of 80% to 125%.

Positive ADA binding status was identified as a significant time-varying covariate on tarlatamab CL. Individuals with positive ADA binding status at any time during the study were estimated to have higher CL. Overall, the impact of ADA on exposures was not clinically relevant as displayed by subgroup analyses for efficacy endpoints in ADA positive and ADA negative subjects.

Race was found to be correlated with central volume of distribution (Vc); however, race had no relevant impact on exposures. Liver function and number of prior lines of therapy were both found to be statistically correlated with tarlatamab CL, however the estimated effects on exposure are not expected to be clinically meaningful.

Significant exposure-response relationships were established for key efficacy measures, including ORR, DCR, best tumor size response (BTSR), progression-free survival (PFS), and OS. Near maximal efficacy was observed at exposures associated with the clinical regimen of 10 mg Q2W. Higher baseline sum of tumor lesion diameter and mild/moderate hepatic impairment were both associated with higher hazard for OS, independent of tarlatamab exposures. As both covariates indicate subjects who have more advanced disease at baseline, it is likely that the identified relationships were driven by an overall prognostic effect on survival rather than tarlatamab exposures

No clear trends for exposure-response relationships were identified for grade ≥ 3 adverse events, grade ≥ 3 treatment-related adverse events, and grade ≥ 3 adverse events of interest of

neurological toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS), and cytokine release syndrome (CRS). A statistically significant trend was observed for higher percentage of subjects experiencing grade ≥ 3 neutropenia with increasing tarlatamab exposures. A higher percentage of Asian subjects are estimated to have grade ≥ 3 neutropenia relative to Caucasian subjects. However, the risk of grade ≥ 3 neutropenia events in Asian subjects was not associated with higher tarlatamab exposures. No clinically relevant impact on QTc interval was observed at the clinical regimen of 10 mg Q2W.

Detailed results are provided in Report 160172 (Population PK Report) (Module 5.3.3.5) and Report 160173 (Exposure-response Analysis Report) (Module 5.3.4.2).

The Applicant's Position:

None of the covariates evaluated in this analysis resulted in clinically meaningful changes in efficacy or safety and therefore do not warrant a dose adjustment.

The FDA's Assessment:

FDA agrees with the Applicant that no dosage modification is needed based on the intrinsic factors assessed in the population PK analyses. The flat E-R relationships, except for positive E-R for Grade ≥3 neutropenia, support that the identified PK variability does not warrant additional dosage modification or mitigation strategies. The effects of severe renal impairment and moderate to severe hepatic impairment on tarlatamab pharmacokinetics are unknown.

6.2.2.3. Outstanding Issues

Data:

Not Applicable.

The Applicant's Position:

None.

The FDA's Assessment:

Not applicable.

6.2.3. General Pharmacology and Pharmacokinetic Characteristics

Data:

Tarlatamab PK were approximately dose-proportional in the evaluated dose range of 0.003 mg to 100 mg IV administered Q2W and 200 mg Q3W. Following the clinical regimen of 1 mg on day 1, then 10 mg on day 8, day 15, and Q2W thereafter, steady state in tarlatamab serum concentrations were approximately achieved by cycle 2 day 15. Tarlatamab mean C_{trough} values at steady state (cycle 2 day 15 predose) and peak serum concentrations at steady state (cycle 2 day 15, end of infusion) were 0.429 μg/mL and 3.83 μg/mL, based on pooled data across phase 1, phase 2, and phase 3 studies. There was no indication of time-dependent kinetics.

Based on cross-study population PK analyses, population mean (%CV) for CL is estimated to be 0.728 L/day (34%). Vss mean (%CV) based on individual parameters is estimated to be 8.53 L (33%) and terminal half-life mean (%CV) is estimated to be 10.6 days (31%)

At the clinical regimen of 10 mg Q2W, treatment emergent ADA incidence was 8.5% (20/234) for Study 20210004, 5.6% (7/125) for the Study 20200491, and 8.2% (7/85) for Study 20160323. An analysis of pooled data from all subjects receiving the 10 mg target dose across Studies 20210004, 20200491, and 20160323 showed that 34 of 444 subjects (7.7%) had developed antitarlatamab binding antibodies. In the phase 2 and phase 3 studies which employed the NAb assay, the NAb incidence was 3.1% (11/359 subjects).

Potential impact of antitarlatamab antibodies on the PK, clinical efficacy, and clinical safety of tarlatamab was assessed with the following results:

- Based on inter-subject comparison, tarlatamab peak and trough serum concentrations (central tendency and distribution) are comparable between subjects who were antidrug antibody (ADA) positive at any time during the study and those who were ADA negative over time. Based on the population PK analysis, tarlatamab clearance was estimated to increase by ~14% in subjects who were ADA positive.
- At the clinical dosing regimen, the efficacy measures (including OS, ORR, DCR, and DOR) were similar for antitarlatamab binding antibody positive subjects compared with those who were antitarlatamab antibody negative.
- The frequency of adverse events, grade 3 or higher events serious adverse events, and were similar between the antitarlatamab-positive subjects and the antibody-negative subjects. In addition, there was no evidence of an impact to safety based on review of adverse events by system organ class and preferred term with antitarlatamab antibodies.

The Applicant's Position:

Across Studies 20160323, 20200491 and 20210004, tarlatamab exhibited approximate dose-proportional increases in exposures in the evaluated dose range. The steady state in tarlatamab serum concentrations were approximately achieved by the start of cycle 2. The model estimated mean (%CV) estimated terminal phase elimination half-life at steady state was 10.6 (31%) days, across the evaluated dose range. The incidence of antitarlatamab antibody development was low. There was no meaningful clinical impact of antitarlatamab antibody development on PK, efficacy or safety.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the established PK characteristics for tarlatamab.

Immunogenicity

FDA generally concurs with the Applicant's immunogenicity assessment. FDA analysis of Study 20210004 yielded an ADA incidence of 9% (21/234) and NAb incidence of 52% (11/21) (Table 4). Across studies, the treatment-emergent ADA incidence is 7.7% in participants who received a dosing regimen of 10 mg Q2W after the step-up doses. The population PK analysis demonstrated an approximately 14% higher clearance in participants with treatment-emergent ADA; no clinically significant differences in efficacy or safety outcomes were observed between ADA positive and negative participants (Table 5).

Table 4. Summary of immunogenicity incidence in Study 20210004

	Number of patients
Overall patients	251
Baseline evaluable patients	247
Baseline ADA+ patients	22
Post-baseline evaluable patients	234
Treatment-emergent ADA+ patients (ADA incidence)	21 (9%)
Treatment-induced ADA (negative at baseline)	18
Treatment-boosted ADA (positive at baseline, post-baseline titer increased by >4 fold)	3
Transient	6
Treatment-induced NAb+ subjects (NAb incidence)	11 (52%)
Transient	0

Source: FDA analysis using dataset adis.xpt and adpc.xpt

Table 5. Summary of efficacy by treatment-emergent ADA in Study 20210004

	TE-ADA-	TE-ADA+		
		Overall	nAb-	nAb+
n	192	21	11	10
ORR, n (%)	82 (43%)	7 (33%)	6 (55%)	1 (10%)
DOR in responders, months	5.6	4.1	3.7	12.4
DCR, n (%)	150 (78%)	18 (86%)	8 (73%)	10 (100%)
OS, months	10.0	9.0	9.3	9.0
PFS, months	4.8	4.1	4.5	3.6

Source: FDA analysis using dataset adis.xpt and er dataset. The median values were provided for DoR, OS, and PFS.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Data from Study 20160323 (phase 1), Study 20200491 (phase 2) and Study 20210004 (phase 3) were included in an integrated exposure-response analysis to support the selection of the clinical dosing regimen (summarized in Section 3.4 of the Clinical Overview and detailed in Section 3.5 of Module 2.7.2, Summary of Clinical Pharmacology). Relationships between tarlatamab exposure and selected measures of response (ORR, DCR, BTSR, PFS, OS, and DOR) were evaluated. The tarlatamab exposure metrics evaluated as predictors of response were model-predicted average concentrations over the first cycle (C_{avg}), peak serum concentrations over the first cycle (C_{max}), and trough serum concentrations at the end of the first cycle on day 28 (C_{trough}), generated using a population PK model. Covariates included in the analyses were demographic factors (age, body weight, sex, race, ethnicity), organ impairment (normal, mild, moderate renal and hepatic function), baseline serum albumin, disease status (ECOG and sum of tumor lesion diameters at baseline), number of prior therapies, and positive ADA status.

With regard to evidence of effectiveness, integrated analysis using pooled data from Study

20160323, Study 20200491, and Study 20210004 show that:

- Significant exposure-response relationships were established for key efficacy measures including ORR, DCR, BTSR, PFS, and OS.
- Near maximal efficacy was observed at exposures associated with the proposed clinical regimen of 10 mg Q2W.
- Exposures associated with lower doses are estimated to have lower efficacy.

The Applicant's Position:

Overall, results of exposure-response analysis for efficacy measures suggest the proposed dosing regimen of 10 mg Q2W exhibited near maximal efficacy in the intended patient population, and exposures associated with lower doses are estimated to have lower efficacy. None of the covariates evaluated in this analysis resulted in clinically meaningful changes in efficacy and therefore do not warrant a dose adjustment.

The FDA's Assessment:

FDA agrees that the results from the clinical pharmacology program (i.e., PopPK, E-R on safety and efficacy, and immunogenicity) provides supportive evidence of effectiveness. Refer to efficacy and safety in Sections 7 and 8, respectively, and popPK, E-R, and immunogenicity assessment on PK in Section 19.4.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:
See Section 6.2.2.1, General Dosing

The proposed dose is effective and generally well tolerated in subjects with advanced SCLC. The proposed dosing regimen is supported by the observed efficacy and safety data and demonstrates a favorable benefit-risk profile. In addition to exposure-response analysis for efficacy, analysis correlating tarlatamab exposures with key safety measures using pooled data from Study 20160323, Study 20200491, and Study 20210004 were performed. No clear trends for exposure-response relationships were identified for grade ≥ 3 adverse events, grade ≥ 3 treatment-related adverse events, and grade ≥ 3 adverse events of interest of neurological toxicity including ICANS, and CRS. A statistically significant trend was observed for higher percentage of subjects experiencing grade ≥ 3 neutropenia with increasing tarlatamab exposures. A higher percentage of Asian subjects are estimated to have grade ≥ 3 neutropenia relative to Caucasian subjects.

However, the risk of grade ≥ 3 neutropenia events in Asian subjects was not associated with higher tarlatamab exposures.

In addition, no clinically relevant impact on QTc interval was observed at the proposed clinical regimen of 10 mg Q2W.

The Applicant's Position:

Overall, results of exposure-response analysis suggest the proposed dosing regimen of 10 mg Q2W exhibited near maximal efficacy with a limited impact on neutropenia and favorable benefit-risk profile in the intended patient population. None of the covariates evaluated in this analysis resulted in clinically meaningful changes in efficacy or safety and therefore do not warrant a dose adjustment.

The FDA's Assessment:

FDA agrees with the proposed recommended dosage of 10 mg Q2W after the step-up doses for the proposed patient population.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

See Section 6.2.2.2, Therapeutic Individualization.

The Applicant's Position:

None of the covariates evaluated in these analyses resulted in clinically meaningful changes in efficacy or safety and therefore no dose adjustment is recommended.

The FDA's Assessment:

FDA agrees that no alternative dosing regimen or management strategy is required based on evaluated intrinsic factors.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Based on molecular size and route of administration of tarlatamab, no formal food-drug or drug-drug interaction studies were required and therefore not performed.

The Applicant's Position:
Not applicable.

The FDA's Assessment:

FDA generally agrees with Applicant's position, with language previously added in Section 12.3 to note the potential risk of IL-6 mediated CYP suppression upon CRS (refer to multi-desciplinary review of BLA 761344).

X	X
Primary Reviewer: Ye Xiong	Secondary Reviewer: Jiang Liu
X	X
Primary Reviewer: Zhe Li	Secondary Reviewer:: Stacy Shord

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:
The clinical studies supporting the marketing application for the intended indication in SCLC are provided in Table 3. The primary study to support efficacy and safety is the pivotal phase 3 Study 20210004.

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Table 6. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Subjects Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
Controlled Studies (Module 5.3.5.1)							
20210004	Efficacy, safety, tolerability, PROs, PK	Phase 3 • randomized • active-controlled • open-label • multicenter	Tarlatamab 1 mg on Day 1, then 10 mg on Day 8, Day 15, and Q2W IV thereafter; Lurbinectedin 3.2 mg/m^2 IV Q3W; Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2/day PO (1.2 mg/m^2 IV or 2.3 mg/m^2/day PO in China) on Days 1 to 5 Q3W cycles; or Amrubicin 40 mg/m^2 IV days 1 to 3 Q3W	509/490 255 participants SOC/254 participants tarlatamab	Adult participants ≥ 18 years of age with SCLC who have progressed after 1 prior line of platinum containing therapy	Approximately 4 years	Ongoing/Full CSR; DCO 29 January 2025

Footnotes are defined on the last page.

Table 3. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Participants Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
Uncontrolled Studies (Module 5.3.5.2)							
20160323	PK, safety, tolerability; MTD or RP2D and preliminary antitumor activity	Phase 1 • nonrandomized • dose exploration • dose expansion • open-label • multicenter	Part A1: Monotherapy dose exploration; Tarlatamab 0.003 to 100 mg IV or eIV Q2W Part A2: Monotherapy dose expansion; Tarlatamab 10 or 100 mg IV or eIV Q2W Part C: Combination dose exploration with fixed dose of pembrolizumab; Tarlatamab 0.1 or 0.3 mg IV Q2W; Pembrolizumab 200 mg IV Q3W Part D: Monotherapy dose with additional CRS mitigation strategies[b]; Tarlatamab 100 mg IV Q2W	269/392 as of 18 October 2024	Participants ≥18 years with SCLC who progressed or recurred following at least 1 platinum-based regimen	Approximately 4 years	Ongoing/ Two Reports: 1. Initial CSR; DCO 28 March 2023 2. Supplemental Primary Analysis CSR; DCO 18 October 2024

Footnotes are defined on the last page.

Table 3. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Participants Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
Study 20160323 (continued)			Part E: Monotherapy administration with 24-hour monitoring; Tarlatamab 100 mg IV Q2W Part F: Monotherapy administration with 8-hour monitoring; Tarlatamab 10 mg IV Q2W Part G: Monotherapy alternative dosing schedule; Tarlatamab 100 mg IV day 1/day 8[c] or 200 mg IV Q3W				
20200491	Efficacy, safety, tolerability, PK	Phase 2 • randomized dose evaluation • nonrandomized dose expansion • open-label (BICR endpoint) • multicenter		222/220	Adult participants [3] 18 years of age with confirmed SCLC who have progressed after treatment with platinum containing therapy, and at least 1 additional line of therapy	Approximately 24 months	Ongoing/ Two reports: 1.Initial Primary Analysis CSR (full); DCO 27 June 2023 2. Supplemental CSR; DCO 18 October 2024

Footnotes are defined on the last page.

Table 3. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Participants Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
Study 20200491 (continued)			Part 1: Tarlatamab 1 mg on Day 1, then 10 or 100 mg on Day 8, Day 15 and Q2W IV thereafter Part 2 and 3: Tarlatamab 1 mg on Day 1, then 10 mg (based on an interim analysis of Part 1) on Day 8, Day 15 and Q2W IV thereafter				

Footnotes are defined on the last page.

Table 3. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Participants Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
Other Studies (Module 5.3.5.4)							
20230016	Efficacy, safety	Phase 3 • randomized • double-blind • placebo-controlled • multicenter	Placebo or Tarlatamab IV 1 mg on Day 1, then 10 mg on Day 8, Day 15 and Q2W thereafter	171/400 as of 24 March 2025	Adult participants ≥ 18 years of age with LS-SCLC who have not progressed after completion of concurrent chemoradiation therapy consisting of platinum (cisplatin or carboplatin), etoposide, and definitive radiation therapy.	Approximately 6 years	Ongoing/Safety Summary Report; DCO 24 March 2025

Footnotes are defined on the last page.

Table 3. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Participants Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
20200041	Efficacy, safety	Phase 3 • randomized • open-label • active-controlled • multicenter	Tarlatamab 1 mg on Day 1, then 10 mg on Day 8, Day 15, and Q2W IV thereafter, Durvalumab 1500mg IV Q4W (for patients with body weight < 30kg, 10mg/kg Q2W)	323/550 as of 24 March 2025	Adult participants [3] 18 years of age with ES-SCLC with ongoing response or stable disease after completion of initial 1L therapy with platinum chemotherapy (carboplatin or cisplatin), etoposide, and durvalumab	Approximately 3 years	Ongoing/Safety Summary Report; DCO 24 March 2025

Footnotes are defined on the last page.

Table 3. Applicant – Table of Clinical Studies

Study Type and Protocol Number	Study Objectives	Study Design and Type of Control	Treatment(s) Administered	Number of Participants Enrolled (Actual/Planned)	Key Entry Criteria	Study Duration Per Protocol	Study Status/ Report Type[a]
20230273	Efficacy, safety, tolerability, PK	Phase 2a • open-label • multicenter • single arm	Tarlatamab 1 mg on Day 1, then 10 mg on Day 8, Day 15, and Q2W IV thereafter	32/30 as of 28 March 2025	Adult participants who were residents in China and of Chinese ancestry, ≥ 18 years of 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	Approximately 24 months; extended as needed to ensure all subjects can be followed in LTFU for at least 1 year after last dose	Ongoing/CRS tables[d]; DCO 28 March 2025

BICR = blinded independent central review; CRS = cytokine release syndrome; CSR = clinical study report; DCO = data cut-off; eIV = extended intravenous; ES = extensive stage; IV = intravenous; LS = limited stage; MTD = maximum tolerated dose; PK = pharmacokinetics; PO = oral; PRO = patient-reported outcome; SOC = standard of care; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; RP2D = recommended phase 2 dose; SCLC = small cell lung cancer.

[a] Status at the time of the marketing application.

[b] Participants received tarlatamab in combination with oral dexamethasone.

[c] Included a 1 mg run-in tarlatamab dose on cycle 1 day 1, stepped up to 100 mg on cycle 1 day 8, and stepped up to the target dose of 100 mg on cycle 1 day 15, and days 1 and 8 of each following cycle (21 day/cycle) at 100 mg.

[d] Full CSR in China

The Applicant's Position:
All studies pertinent to the evaluation of efficacy and safety for the intended indication are summarized above in Table 3. The primary support for the efficacy of the proposed indication is based on the results from pivotal phase 3 Study 20210004 (DeLLphi-304) in subjects with relapsed SCLC after platinum-based first-line chemotherapy.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Patients from DeLLphi-304 (Study 20210004) comprise the primary efficacy population to support efficacy evaluation in Section 14 of the label and the safety population in Section 6 of the label for this application. The efficacy data submitted represent the first interim analysis (IA1) of OS and is from a data cut off (DCO) date of January 29, 2025. Patients from DeLLphi-300 (Study 20160323; n=88), DeLLphi-301 (Study 20200491; n=133) and DeLLphi-304 (Study 20210004; n=252) treated with the labeled dose of tarlatamab comprise the primary safety population use to support labeling for Section 5.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 20210004

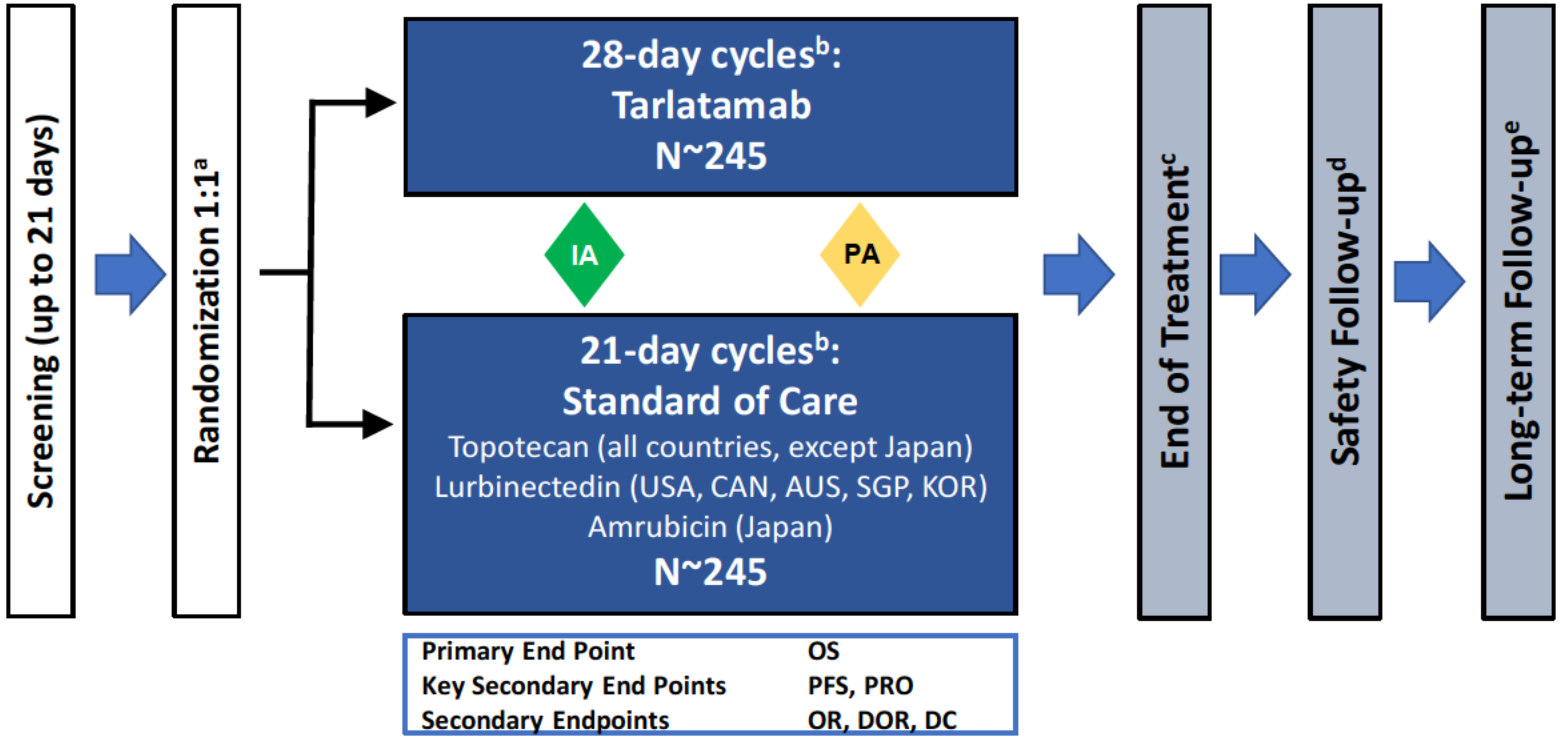
Trial Design

The Applicant's Description:

Study 20210004 is an ongoing open-label, randomized, multi-center, phase 3 study that evaluated the efficacy and safety of tarlatamab compared with standard of care (SOC) chemotherapy for the treatment of subjects with SCLC who have progressed after 1 prior line of platinum-containing therapy.

The study consists of a 21-day screening period, a treatment period, a safety follow-up visit, and a long-term follow-up period. Subjects were randomized with a 1:1 allocation ratio to receive tarlatamab or SOC therapy (lurbinectedin or topotecan in the US, Canada, Australia, Singapore, Korea; amrubicin in Japan; topotecan in all countries except Japan). Subjects received study treatment until investigator-determined radiographic disease progression per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), unacceptable toxicity, withdrawal of consent, death, or end of study as determined by the sponsor (whichever occurs first). Following documented radiographic progression, the subject had the option to remain on study treatment provided certain criteria were met.

Figure 1. Applicant – Schema of Study 20210004



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

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

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

[c] End of Treatment visit occurs at the time the decision is made to discontinue study treatment and prior to start of new anti-cancer treatment.
[d] Safety Follow-up visit occurs approximately 60 (+5) days after last study treatment administration.
[e] Long-term follow-up for survival occurs approximately every 12 weeks (± 14 days) after the SFU visit, or last imaging visit, whichever is later, for up to 3 years from last subject enrolled, or 1 year from the subject's last dose of study treatment, whichever is later.

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The FDA's Assessment:

FDA agrees with the Applicant's description of the DeLLphi-304 trial design.

Eligibility Criteria

The Applicant's Description:

Eligible subjects were ≥ 18 years (or legal adult age within country, whichever is older) with histologically or cytologically confirmed relapsed SCLC who progressed following 1 platinum-based regimen. Once consented to the study, subjects underwent protocol-required screening assessments to confirm all eligibility requirements of the study have been met. Subjects were required to have measurable lesions as defined per RECIST 1.1 within the 21-day screening period and adequate organ function.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of key eligibility criteria for DeLLphi-304. Additional key inclusion criteria include patients having an ECOG performance status of 0 or 1 and at least one measurable lesion as defined by RECIST v1.1. Key exclusion criteria included patients with symptomatic brain metastases or with active immunodeficiency.

Study Endpoints

The Applicant's Description:

The primary objective of the study was to compare the efficacy of tarlatamab with SOC on prolonging OS. Key secondary objectives included comparing the efficacy of tarlatamab with SOC as assessed by:

- progression-free survival based on investigator assessment per RECIST 1.1
- patient-reported disease-related symptoms, physical function, and quality of life

Secondary endpoints included other measures of efficacy (PFS at 1 year from randomization, ORR, disease control, DOR, and OS at 1, 2, and 3 years from randomization), safety, PK, immunogenicity, and other measures of patient-reported outcomes.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of study endpoints. In general OS is a relevant endpoint to evaluate the treatment effect of tarlatamab in this patient population and disease setting. Key secondary endpoints based on patient reported outcomes (PROs) were collected through EORTC QLQ-C30 and EORTC QLQ-LC13 instruments and included dyspnea (a composite score derived from QLQ-

C30 Question 8 and QLQ-LC13 Questions 3 to 5), cough (single item: QLQ-LC13 Question 1), chest pain (single item: QLQ-LC13 Question 10), physical functioning (a composite score derived from QLQ-C30 Questions 1 to 5) and global health status (a composite score derived from QLQ-C30 Questions 29 and 30). PRO-based endpoints were assessed as mean change from baseline through week 18.

(b) (4)

Statistical Analysis Plan and Amendments

The Applicant's Description:

There were 4 amendments to the original statistical analysis plan (SAP) before the data snapshot date of this report (17 March 2025), as summarized in Table 4. Within these SAP amendments, there were no changes to the protocol-specified analyses. The efficacy endpoints and the corresponding statistical methods of analysis for Study 20210004 are summarized in Table 5.

Table 7. Applicant - Summary of Statistical Analysis Plan Amendments

Amendment	Changes
Original (v1.0) 10 May 2023	Not applicable
Amendment 1 (v2.0) 19 March 2024	• updated objective and endpoints and removed exploratory endpoints • updated study design along with study schema • updated sample size • updated planned covariate and subgroups • updated definition section for TEAE, TTR and added definitions for chemotherapy-free interval, relative dose intensity • added definition for PRO analysis set • updated planned analyses for interim analysis and early stopping guidelines and primary analysis • updated handling of missing and incomplete data

	• updated general considerations and primary efficacy endpoint and secondary efficacy endpoint summary of statistical methods of analysis and added column for sensitivity analysis • added sensitivity analysis • updated analysis of primary efficacy endpoint • updated exposure to other protocol-required therapy and analysis of biomarker endpoint
Amendment 2 (v3.0) 01 August 2024	• added study design for safety follow-up period • updated covariates and subgroups for collapsed strata and additional subgroups

Footnotes are defined on the last page.

Table 4. Applicant - Summary of Statistical Analysis Plan Amendments

Amendment	Changes
	• updated definitions for baseline, BOR, safety follow-up, study day 1 and TEAE • updated primary analysis for estimated PFS events by timing of OS primary analysis • updated general considerations for collapsed strata and PRO endpoint analysis details • updated demographics and baseline characteristics • updated efficacy analysis • updated adverse events, laboratory test results, and ECG • updated Appendix A for partial or missing new anti-cancer therapy initiation date and Appendix B (BOR calculation algorithm)
Amendment 3 (v4.0) 24 October 2024	• updated DLL3 subgroup analysis and criteria for subject count in subgroup analysis • updated adverse events

Amendment 4 (v5.0) 21 November 2024	• removed 'disease stage (limited stage vs extensive stage) • removed additional subgroup analysis comparing tarlatamab to topotecan/amrubicin and lurbinectedin separately, which was documented in a separate SSAP • updated censoring rule for PFS sensitivity analysis • added the details of adverse events of interest • removed analysis of exposure to non-investigational product • Updated Appendix A for imputation rules for partial or missing new anti-cancer therapy initiation date

BOR = best overall response; DLL3 = delta-like ligand 3; ECG = electrocardiogram; IP = investigational product; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-report outcomes; SSAP = supplemental statistical analysis plan; TEAE = treatment-emergent adverse event; TTR = time-to-response

Table 8. Applicant - Statistical Methods of Analysis for Study 20210004

APPEARS THIS WAY ON ORIGINAL

Endpoint	Statistical Analysis Methods
OS	The primary inferential comparisons of the OS primary endpoint between tarlatamab and SOC arms was made using a stratified log-rank test controlling for the randomization stratification factors, using the intent-to-treat (ITT) analysis set. The HR and its 95% CI was estimated using a Cox proportional hazards model stratified by the randomization stratification factors.
PFS	PFS was analyzed using the same approach as OS. The PFS rate at 1 year was reported with the 95% CI.
PRO	
• Chest pain	The ordinal endpoint of change from baseline after 18 weeks in symptoms of chest pain, as measured by a single question from QLQ-LC13, was analyzed using a generalized linear mixed model (GLMM) for repeated measures with cumulative logit link.
• Cough	The ordinal endpoint of change from baseline after 18 weeks in symptoms of cough, as measured by a single question from QLQ-LC13, was analyzed using a GLMM for repeated measures with cumulative logit link.
• Dyspnea (Composite Score)	The continuous endpoint of change from baseline after 18 weeks in symptoms of dyspnea was measured by a multiple item dyspnea scale from QLQ-C30 and QLQ-LC13 Symptom Scores. The inferential comparison was made using a mixed model for repeated measurement (MMRM) with a restricted maximum likelihood-based (REML) estimation method with 'unstructured (UN)' covariance structure.
• Physical function	The continuous endpoint of change from baseline after 18 weeks in physical function was measured by QLQ-C30 multi-item scale scores. The inferential comparison was made using an MMRM with a REML estimation method with UN covariance structure.
• Global Health Status	The continuous endpoint of change from baseline after 18 weeks in global health status was measured by QLQ-C30 multi-item scale scores. The inferential comparison was made using an MMRM with a REML estimation method with UN covariance structure.
• Pain	The continuous endpoint of change from baseline in pain after 18 weeks, as measured by the Brief Pain Inventory -- Short Form (BPI-SF) Item 3, pain at its worst, was compared using a MMRM approach with a REML estimation method with UN covariance structure.
• Remaining domains for QLQ-C30 and QLQ-LC13	The change from baseline after 18 weeks for the remaining domains was compared using an MMRM with a REML estimation method with UN covariance structure for continuous endpoints and GLMM with cumulative logit link for ordinal endpoints.

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Footnotes defined on last page of this table.

Table 5. Applicant - Statistical Methods of Analysis for Study 20210004

Endpoint	Statistical Analysis Methods
• Patient Global Impression of Severity (PGIS) (overall and for chest pain, cough, dyspnea, physical function, and global health status)	The continuous endpoint of change from baseline after 18 weeks in PGIS was compared using an MMRM with a REML estimation method with UN covariance structure.
• Patient Global Impression of Change (PGIC) (overall and for chest pain, cough, dyspnea, physical function, and global health status)	Summary scores at each assessment and change from baseline after 18 weeks of the continuous endpoint of visual analogue scale (VAS) score as measured by 5-level EuroQol-5 Dimension (EQ5D-5L) were assessed using an MMRM with a REML estimation method with UN covariance structure.
ORR	ORR was analyzed using the Cochran-Mantel-Haenszel chi-square test controlling for the randomization stratification factors. An estimate of the common odds ratio (95% CI) was provided as a measure of the relative treatment effect. The ORR was calculated and the 95% CI was estimated using the Clopper-Pearson method.
DOR	The descriptive analysis of DOR was provided using the same methods as OS.
DCR	DCR was analyzed using the same method as described for the ORR endpoint.

BPI-SF = Brief Pain Inventory – Short Form; DCR = disease control rate; DOR = duration of response; EORTC-QLQ-LC13 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13; EQ5D-5l = 5-level EuroQol-5 Dimension; GLLM = generalized log-linear model; HR = hazard ratio; ITT = intent to treat; MMRM = mixed model for repeated measurement; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcomes; SOC = standard of care; VAS = visual analog scale

The FDA's Assessment:

FDA agrees with the Applicant's description of SAP amendments and statistical analysis methods for primary and secondary endpoints.

With SAP amendment 1, reflecting protocol amendment 2 (dated September 6, 2023) the sample size was reduced from 700 to 490 patients based on external data from Study 20200491. An interim futility analysis based on ORR was also removed. FDA did not object to this change as the sample size change was driven by external information and no analysis was performed prior to this change.

OS is to be analyzed using a stratified log rank test controlling for the randomization stratification factors. OS final analysis is triggered at 345 deaths with an interim analysis planned at 75% information fraction, or 259 deaths. This

plan provides 91% power to detect a hazard ratio of 0.7 at two-sided alpha of 0.05. While there are four stratification factors - prior anti-PD-(L)1 exposure, chemotherapy-free interval (CFI) (≥ 180 days; < 180 to ≥ 90 days; < 90 days), presence (previous or current) of brain metastases, and standard of care - SAP amendment 2 specified that to prevent overstratification, only presence (previous or current) of brain metastases (yes or no) and chemotherapy-free interval (collpased into < 90 days and ≥ 90 days) would be included in stratified analyses.

Key secondary endpoints PFS by investigator per RECIST v1.1 and multiple PRO-based endpoints are to be tested hierarchically if OS is statistically significant. While testing of PFS is predicated upon a statistically significant test of OS, the maximum number of events for the PFS analysis is 456 and testing of PFS at the OS IA will be adjusted by Lan-DeMets alpha spending function with Pocock bounds using actual number of PFS events observed.

In addition to the main SAP, there are two supplemental SAPs:

Supplemental SAP for Key Secondary and Secondary Patient Reported Outcome (PRO) Analysis was submitted to FDA on October 25, 2024, and subsequently amended on January 16, 2025. PRO-based endpoints are to be tested hierarchically in two levels; dyspnea, cough and pain are tested first using the Holm's procedure. If all three are statistically significant, the second level of PRO-based endpoints, physical functioning and global health score, will then both be tested using the Holm's procedure

Supplemental SAP for Assessment of Proportional Odds Assumption for Ordinal PRO Endpoints was submitted to FDA on April 30, 2025. This supplemental SAP addressed FDA's concern regarding potentially biased results when testing the PRO-based endpoints of cough and chest pain in an ordinal proportional odds model if the proportional odds assumption is violated.

Protocol Amendments

The Applicant's Description:

Changes in the conduct of pivotal Study 20210004 that were implemented by protocol amendments are described in the protocol. Major changes in the conduct of the study are described in Table 6.

Table 9. Applicant – Protocol Amendment Summary

Amendment	Changes

Original 09 December 2022	Not applicable
Protocol Amendment 1 30 May 2023	• Provided additional language to clarify the purpose for having an optional prescreening phase in the study • Specified that serum pregnancy test at screening must be performed within 7 days of cycle 1 day 1 and all additional pregnancy tests (serum or urine) must be performed at day 1 of each cycle and reviewed before treatment administration • Updated eligibility criteria for subjects who have progressed or recurred following 1 platinum-based regimen to add that only subjects who, per investigator discretion, are candidates for the 3 standard of care therapies should be included • Added that after completion of tarlatamab treatment, live and live-attenuated vaccines are prohibited for 42 days after last dose of tarlatamab • Updated tarlatamab dose modification guidelines for adverse events to: • Add specific guidelines for administration of corticosteroids by specifying dosing of corticosteroids (8 mg to 16 mg of dexamethasone or equivalent) and frequency of administration (every 8 hours) to manage neurologic events • Clarify that for neurological events grade 4, tarlatamab administration must be permanently discontinued rather than interrupted/delayed
Protocol Amendment 2 06 September 2023	• Removed the requirement of prescreening period and tissue biopsy with an all-comers strategy • Updated the statistic assumption and the number of subjects to 490 subjects, approximate number of sites to 240, and total study duration to approximately 4 years • Removed the requirement for hospitalization postinfusion and replaced with reduced monitoring guidance • Updated the topotecan (China) intravenous dose to 1.2 mg/m2 or other locally approved dose

Footnotes are defined on the last page.

Table 6. Applicant – Protocol Amendment Summary

Amendment	Changes

	• Updated the schedule of activities table:
	  • to remove prescreening (archival tumor tissue/biopsy), C-reactive protein, ferritin, and endocrine panel
	  • to add demographics information, prior therapies review, thyroid stimulating hormone, free T4 assessments, and tumor tissue collection assessments
	  • to update physical examination to inform that weight must be collected at each day 1, vital signs and pulse oximetry, and pharmacokinetic and antitarlatamab antibody collection windows
	  • to update urinalysis, 12-lead electrocardiogram (ECG), hematology, and chemistry panel assessments
	• Removed exploratory objectives and endpoints
	• Updated the inclusion/exclusion criteria:
	  • to include subjects with histologically or cytologically confirmed small cell lung cancer (SCLC) with demonstrated progression or relapse
	  • to include subjects with prothrombin time (PT)/international normalized ratio (INR) and partial thromboplastin time (PTT) or activated partial thromboplastin time (APTT) ≤ 1.5 x institutional upper limit of normal (ULN) except for subjects undergoing oral anticoagulation using vitamin K antagonists
	  • to clarify that subjects must be on a stable dose of anticoagulant therapy for 2 weeks prior to enrollment
	  • to exclude subjects with prior therapy with tarlatamab or any of the standard of care (SOC) chemotherapy included as part of this trial or in any tarlatamab clinical trial

Protocol Amendment 3 11 December 2023	• Updated the safety monitoring guidelines (6-8 hours post infusion on C1D1 and C1D8) to ensure subject safety when receiving tarlatamab, in alignment with data presented to and in agreement with regulatory agencies. • Updated the collection of patient reported outcomes to include an indication of taste changes, in agreement with regulatory agencies • Updated the study rationale, dose justification, and benefit/risk profile based on the latest data regarding antitumor activity in subjects with extensive stage small cell lung cancer (ES-SCLC) in a phase 2 (Study 20200491) and phase 1 study (Study 20160323)

Footnotes are defined on the last page.

Table 6. Applicant – Protocol Amendment Summary

Amendment	Changes

	• Updated the Schedule of Activities to ensure assessment timing and collection is performed as intended to achieve the goals of the study (Section 1.3) • Updated the eligibility criteria for stricter guidance on hepatitis B and C exclusion criteria • Updated the eligibility criteria on brain metastasis exclusion criteria • Updated the eligibility criteria with clarification on "mixed histology" exclusion criteria. • Updated in the recommendation guidelines for the management of CRS to include the consideration for administration of dexamethasone in grade 1 and 2 CRS • Removed language that disease progression of SCLC and death due to disease progression are not considered and reported as adverse events or serious adverse events as this does not apply to studies that are ongoing
Protocol Amendment 3 Superseding 14 December 2023	• Added a collection of tumor tissue (at screening and end of treatment) to the standard of care schedule of activities
Protocol Amendment 4 19 July 2024	• Updated language for subjects with no exposure to prior anti-programmed cell death ligand 1 (PD-L1) to include the classification for non-use. • Added language to specify that ad hoc vital status (survival status) collection may be required to support key study analysis. • Updated the safety follow-up (SFU) period from 42 (+5) days. • Clarified the time points for collecting PK and antibody samples. • Specified that serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen during the long-term follow-up phase. • Clarified collection timepoints by adding a window of ± 7 days in every 6 week visit to allow collection of Paxgene RNA, circulating tumor DNA (ctDNA), and patient-reported outcomes (PRO) and health economic assessments on the same visit • Updated the radiological imaging and tumor assessment period to ±7 days • Updated the timeframe for using contraception following the last dose of tarlatamab throughout the protocol.

Footnotes are defined on the last page.

Table 6. Applicant – Protocol Amendment Summary

Amendment	Changes
	• Updated monitoring guidance to include details for cycle 2+ • Revised the language for live and live-attenuated vaccines to depict that they are prohibited for a further 60 days after last dose • Revised language regarding treatment; post progression to clarify this is permitted for the standard of care am as well and removed the requirement for radiation therapy • Clarified the action required for step-dose rechallenge after tarlatamab delay • Revised the language for discontinuation of study treatment to clarify that a minimal vital status should be collected. • Revised the language for subject discontinuation/withdrawal from the study to clarify that the subject is not considered to have ended the study until there is no means to continue collection of vital status. • Clarified the actions to be taken if a subject fails to return to the clinic for a required study visit. • Updated end of treatment and SFU language to clarify that a subject at a minimum should be followed for survival and/or the commencement of subsequent cancer therapy. • Added information about hypersensitivity reactions based on the latest available data. • Aligned the AE grading scale to be used for CRS and ICANS

AE = adverse event; APTT = activated partial thromboplastin time; C = cycle; CRS = cytokine release syndrome; ctDNA; circulating tumor DNA D = day; ECG = electrocardiogram; ES-SCLC = extensive stage small cell lung cancer; ICANS = immune effector cell-associated neurotoxicity syndrome; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; PRO = patient-reported outcomes; PT = prothrombin time; PTT = partial prothrombin time; Q6W = every 6 weeks; SFU = safety follow-up; SCLC = small cell lung cancer; ULN = upper limit of normal

The FDA's Assessment:

FDA agrees with the Applicant's description of the protocol amendments. As part of protocol amendment 3, the monitoring guidelines were updated from 48 hours to 6 to 8 hour monitoring. However, only a small number of patients (n=43) were randomized to receive tarlatamab with 6 to 8 hour monitoring.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

Audits of Study 20210004 were included as part of the independent Amgen Quality, Compliance, and Audit program performed by Amgen. The audit certificates for this study are provided in Section 16.1.8 of Study 20210004 clinical study report (CSR).

The Applicant's Position:

Study 20210004 was conducted in accordance with the Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP). Study 20210004 was conducted under Investigational New Drug 134859.

The FDA's Assessment:

FDA agrees with the Applicant's position. Based on the information provided in this application, the conduct of DeLLphi-304 was consistent with the International Council for Harmonization guidelines for Good Clinical Practice, U.S. Federal regulations and requirements by other applicable regulatory authorities.

Financial Disclosure

Data:

See Appendix 19.2.

The Applicant's Position:

Study 20210004 was Amgen-sponsored clinical study. Financial interests or arrangements with clinical investigators have been disclosed (see Appendix 19.2.).

The FDA's Assessment:

The integrity of DeLLphi-304 data was not affected by the financial interests of the Investigators. Please see further assessment of this by FDA in Section 19.2

Patient Disposition

Data:

Overall, as of the data cutoff date of 29 January 2025, 509 subjects were randomized to tarlatamab (254 subjects) or SOC (255 subjects; including 47 lurbinectedin, 208 topotecan/amrubicin). A total of 252 subjects (99.2%) in the tarlatamab group received at least 1 dose of tarlatamab and were included in the safety analysis set. In the SOC chemotherapy group, the safety analysis set included 244 subjects.

As of the data cutoff date, 17.3% of subjects overall were continuing treatment: 27.2% in the tarlatamab 10 mg group and 7.5% in the SOC group. Overall, 80.2% subjects had discontinued investigational product: 72.0% from the tarlatamab 10 mg group, and 88.2% from the SOC chemotherapy. The most common reason for discontinuation in both treatment groups was disease progression (59.8% tarlatamab, 62.4% SOC chemotherapy) followed by death (6.3% tarlatamab, 7.5% SOC chemotherapy). As of the data cutoff date, 51.9% of subjects had discontinued the study: 43.7% from the tarlatamab 10 mg group, and 60.0% from the SOC chemotherapy. The most common reasons for study discontinuation were death (43.7% tarlatamab, 59.2% SOC chemotherapy), followed by withdrawal of consent (0.8% SOC chemotherapy).

The Applicant's Position:

As of the data cutoff date for the supplemental Biologics License Application (sBLA), 509 subjects were enrolled and randomized to tarlatamab (254 subjects) or SOC chemotherapy (255 subjects; including 47 lurbinectedin, 208 topotecan/amrubicin) in Study 20210004. The primary analysis (first planned OS interim analysis) for the pivotal study was based on the ITT Analysis Set which included all subjects who were randomized. Safety analyses included subjects who received at least 1 dose of investigational product.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of patient disposition for DeLLphi-304. Of note, there were 11 (4.3%) patients in the SOC arm compared to 2 (0.8%) patients in the tarlatamab arm who did not receive treatment following randomization. Although slightly imbalanced, the number of patients who did not receive treatment after randomization was not considered high enough to be of concern to the efficacy results, particularly as the primary endpoint of the trial was OS and these patients were still followed for survival status. Of the 11 patients who did not receive treatment after randomization in the SOC arm, 2 had AEs prior to first dose that precluded them from starting treatment (Grade 2 seizures and Grade 3 cholestasis).

Protocol Violations/Deviations

Data:

As of the data cutoff date of 29 January 2025, a total of 172 subjects (33.8%) had 266 important protocol deviations (IPDs). Overall, the most frequently reported (> 5.0% of subjects overall) IPDs were off-schedule important pre-dose safety labs (6.7%) and informed consent form consent (5.7%).

The Applicant's Position:

The above mentioned IPDs did not affect the overall results of the study.

The FDA's Assessment:

FDA reviewed the full list of protocol deviations provided by the Applicant. Overall, 39% of patients in the tarlatamab arm had important protocol deviations compared to 29% of patients in the SOC arm. The number of eligibility criteria violations were similar between treatment arms (7% in the tarlatamab arm vs. 8% in the SOC arm). Overall, the higher number of deviations in the tarlatamab were driven by a higher number of patients with off schedule procedures in the tarlatamab arm (19%, including important pre-dose safety labs unavailable in 13% of patients) vs. SOC arm (10%)

FDA's assessment is that the important protocol deviations are unlikely to have impacted the study's results in a meaningful way.

Table of Demographic Characteristics

Data:

Baseline demographics were generally consistent between the tarlatamab and SOC groups (Table 7). Overall, 69.0% of subjects were men, and the majority were White (57.2%) and not Hispanic or Latino (52.7%). The median (range) age was 65 (20 to 86) years, and the majority of subjects were younger than 65 years (47.9%).

Table 10. Applicant – Baseline Demographics (ITT Analysis Set)

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Overall (N = 509)
Sex - n (%)			
Male	169 (66.3)	182 (71.7)	351 (69.0)
Female	86 (33.7)	72 (28.3)	158 (31.0)
Race - n (%)			
Asian	107 (42.0)	97 (38.2)	204 (40.1)
Black or African American	3 (1.2)	2 (0.8)	5 (1.0)
White	139 (54.5)	152 (59.8)	291 (57.2)
Ethnicity - n (%)			
Hispanic or Latino	11 (4.3)	12 (4.7)	23 (4.5)
Not Hispanic or Latino	128 (50.2)	140 (55.1)	268 (52.7)
American Indian or Alaska Native	1 (0.4)	1 (0.4)	2 (0.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (1.2)	1 (0.4)	4 (0.8)
Missing	2 (0.8)	1 (0.4)	3 (0.6)
Age (years)			
n	255	254	509
Mean	64.2	63.6	63.9

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Overall (N = 509)
SD	9.2	9.4	9.3
Median	66.0	64.0	65.0
Q1, Q3	58.0, 70.0	58.0, 70.0	58.0, 70.0
Min, Max	26, 84	20, 86	20, 86
Age group - n (%)			
18 - 64 years	115 (45.1)	129 (50.8)	244 (47.9)
65 - 74 years	115 (45.1)	95 (37.4)	210 (41.3)
75 - 84 years	25 (9.8)	28 (11.0)	53 (10.4)
≥ 85 years	0 (0.0)	2 (0.8)	2 (0.4)
Region - n (%)			
North America	15 (5.9)	13 (5.1)	28 (5.5)
Europe	113 (44.3)	127 (50.0)	240 (47.2)
Asia	110 (43.1)	97 (38.2)	207 (40.7)
Rest of the world	17 (6.7)	17 (6.7)	34 (6.7)

Data snapshot date: 13 March 2025; Data cutoff date: 29 January 2025.

N = Number of subjects in the analysis set; n = Number of subjects with observed data; Q1 = first quartile; Q3 = third quartile;
Source: Table 14-2.1.1 of Study 20210004.

The Applicant's Position:

Overall, the subjects with SCLC enrolled in pivotal phase 3 Study 20210004 had baseline demographics indicative of subjects with extensive-stage SCLC with progression after 1 prior line of platinum-containing therapy, and are considered to be representative of the overall population of patients with SCLC, (b) (4). Data from racial or ethnic minorities such as American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander are limited.

The FDA's Assessment:

The distribution of the efficacy population across relevant patient demographics was generally similar between arms. While demographics in the DeLLphi-304 study do not completely align with demographics of those of the U.S. patient population with SCLC, as discussed below, the results of DeLLphi-304 are considered applicable to the U.S. population of patients.

Patient enrollment was global; the countries with the highest proportions of patient enrollment were: China (20%), Turkey (11%) and South Korea (11%). Approximately 5% of the patient population was randomized from the United States. However, only 1% of patients in the overall study population were Black/African American. This underrepresents the proportion of Black/African American patients in the U.S., who

comprise about 9% of the U.S. patient population with SCLC (SEER database). A PMC was issued at the time of the initial approval of tarlatamab for an integrated analysis from ongoing, completed, or planned clinical trials and other potential data sources as appropriate enrolling a sufficient representation of U.S. racial and ethnic minority patients that is reflective of the U.S. population of patients with SCLC, to further characterize the efficacy, safety and pharmacokinetics of tarlatamab in these patients; this PMC remains open. (b) (4)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Overall, subjects had a median (range) of 1.0 (1 to 3) prior lines of therapy, including prior PD-1 or PD-L1 (70.7%) and prior radiotherapy (62.9%), and 286 subjects (56.2%) had a chemotherapy-free interval of ≥ 90 days. Most subjects had metastatic disease (91.0%), with brain metastases (44.8%) or liver metastases (35.2%), and an ECOG score of 1 (67.2%). Baseline characteristics were generally consistent between the groups (Table 8).

Table 11. Applicant - Baseline Disease Characteristics (ITT Analysis Set)

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Overall (N = 509)
ECOG status at baseline[a] - n (%)			
0	80 (31.4)	83 (32.7)	163 (32.0)
1	173 (67.8)	169 (66.5)	342 (67.2)
2	2 (0.8)	2 (0.8)	4 (0.8)
Smoking history - n (%)			
Never	31 (12.2)	23 (9.1)	54 (10.6)
Current	51 (20.0)	54 (21.3)	105 (20.6)
Former	173 (67.8)	177 (69.7)	350 (68.8)
Prior lines of therapy - n (%)			
1	248 (97.3)	249 (98.0)	497 (97.6)
≥2	7 (2.7)	5 (2.0)	12 (2.4)
Number of prior lines of therapy			
n	255	254	509
Mean	1.0	1.0	1.0
SD	0.2	0.1	0.2
Median	1.0	1.0	1.0
Q1, Q3	1.0, 1.0	1.0, 1.0	1.0, 1.0
Min, Max	1, 3	1, 2	1, 3
Prior PD-1 or PD-(L)1 inhibitor therapy - n (%)			
Yes	180 (70.6)	180 (70.9)	360 (70.7)
No	75 (29.4)	74 (29.1)	149 (29.3)
Prior radiotherapy for current malignancy - n (%)			
Yes	161 (63.1)	159 (62.6)	320 (62.9)
No	94 (36.9)	95 (37.4)	189 (37.1)
Prior surgery for current malignancy - n (%)			
Yes	26 (10.2)	26 (10.2)	52 (10.2)
No	229 (89.8)	228 (89.8)	457 (89.8)
Disease stage at screening - n (%)			
Stage 0	0 (0.0)	0 (0.0)	0 (0.0)
Stage I	0 (0.0)	0 (0.0)	0 (0.0)
Stage II	2 (0.8)	0 (0.0)	2 (0.4)
Stage III	18 (7.1)	21 (8.3)	39 (7.7)
Stage IV	235 (92.2)	233 (91.7)	468 (91.9)

Footnotes on last page

Table 8. Applicant - Baseline Disease Characteristics (ITT Analysis Set)

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Overall (N = 509)
Metastatic at baseline - n (%)			
Yes	236 (92.5)	227 (89.4)	463 (91.0)
No	19 (7.5)	27 (10.6)	46 (9.0)
Chemotherapy-free interval - n (%)			
<90 days	114 (44.7)	109 (42.9)	223 (43.8)
≥90 days	141 (55.3)	145 (57.1)	286 (56.2)
≥90 and <180 days	78 (30.6)	85 (33.5)	163 (32.0)
≥180 days	63 (24.7)	60 (23.6)	123 (24.2)
Brain metastases (previous or current) at baseline - n (%)			
Yes	115 (45.1)	113 (44.5)	228 (44.8)
No	140 (54.9)	141 (55.5)	281 (55.2)
Liver metastases at baseline - n (%)			
Yes	95 (37.3)	84 (33.1)	179 (35.2)
No	160 (62.7)	170 (66.9)	330 (64.8)
DLL3 positive - n/N1 (%)[b]	198/214 (92.5)	207/217 (95.4)	405/431 (94.0)
DLL3 cutpoints - n (%)			
<75% at 2+ and 3+ staining intensity	114 (44.7)	119 (46.9)	233 (45.8)
≥75% at 2+ and 3+ staining intensity	100 (39.2)	98 (38.6)	198 (38.9)
<25% at 2+ and 3+ staining intensity	52 (20.4)	52 (20.5)	104 (20.4)
≥25% at 2+ and 3+ staining intensity	162 (63.5)	165 (65.0)	327 (64.2)
Missing	41 (16.1)	37 (14.6)	78 (15.3)

Page 2 of 2

DLL3 = delta-like ligand 3; ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; N = Number of subjects in the analysis set; N1 = Number of subjects with nonmissing DLL3 results; n = Number of subjects with observed data; Q1 = first quartile; Q3 = third quartile;

[a] 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work; 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours

Patients with ECOG status of 2 were assessed at randomization/day 1 instead of screening

DLL3 positive is defined as subjects with 0+ staining intensity < 100

[b] The percentage for DLL3 positive is based on subjects with nonmissing DLL3 results as denominator

Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025

Source: Modified from Table 14-2.2.1 of Study 20210004

The Applicant's Position:

Overall, the subjects with SCLC enrolled in pivotal phase 3 Study 20210004 had baseline characteristics indicative of subjects with extensive-stage SCLC and are considered to be representative of the overall population of patients with SCLC (b) (4)

The FDA's Assessment:

FDA generally agrees with the Applicant's position/characterization of baseline disease characteristics. All patients had extensive stage disease at baseline, of whom 91% had metastatic disease. All patients had received prior platinum-based chemotherapy with 71% of patients also having received prior anti-PD-(L)1 therapy. Baseline disease characteristics were generally balanced across treatment arms. Via an information request (IR), 7% of patients had no DLL3 staining of intensity 2+/3+.

Eligibility specified patients could have ECOG Performance Status (PS) 0 or 1; however, 4 patients with ECOG PS 2, two on each arm, were enrolled and treated, without protocol deviation being noted. In response to an IR (9/15/2025), the Applicant confirmed that the 4 patients had ECOG of 1 at the time of screening, but ECOG PS had worsened by time of pre-treatment baseline.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

When subjects were dosed at the site, they received study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic was recorded in the source documents and in the case report form (CRF). Additional details on the method used to assess treatment compliance are provided in Protocol Section 6.6.

Concomitant Medications

Throughout the studies, investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Protocol Section 6.1.6 of Study 20210004.

Overall, concomitant medication use was reported for 251 subjects (99.6%) in the tarlatamab group and 242 subjects (99.2%) in the SOC chemotherapy group. The concomitant medications with the use ≥ 10% of subjects are presented in Table 12-14 of Study 20210004. Of these in the tarlatamab group, the most common (≥ 20% of subjects) were paracetamol (68.3%), dexamethasone (31.7%), sodium chloride (27.0%), and lactulose (21.0%). Of these in the SOC chemotherapy group, the most common

(≥ 20% of subjects) were dexamethasone (54.5%),paracetamol (36.1%), ondansetron (32.0%), filgrastim (29.5%), dexamethasone sodium phosphate (23.0%), and pegfilgrastim (22.1%). Concomitant CRS medication use by preferred term is provided in Table 14-8.5.1 of Study 20210004.

Rescue Medication

Not applicable

The Applicant's Position:

No formal treatment compliance measurements were planned. Concomitant medication use was consistent with protocol-specified criteria.

The FDA's Assessment:

FDA agrees with the Applicant's description of treatment compliance along with concomitant and rescue medications. In addition, pretreatment with dexamethasone within 1 hour prior to administration of tarlatamab and treatment with 1 liter of normal saline over 2 to 4 hours on Cycle 1 Day 1 and Day 8 was required for all patients per protocol.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

A total of 509 subjects (tarlatamab: 254 subjects and SOC chemotherapy: 255 subjects) were included in the ITT Analysis Set. The key efficacy results from the phase 3 Study 20210004 (ITT analysis set) are provided in Table 9.

The primary endpoint was OS, defined as the time from randomization until death from any cause. The primary estimand was hazard ratio (HR) of OS between tarlatamab and SOC, for subjects with relapsed SCLC after platinum-based first-line chemotherapy, regardless of subsequent anti-cancer therapy (treatment policy strategy).

The primary endpoint of OS met statistical significance for superiority of tarlatamab compared to SOC. A total of 263 deaths (OS events) were reported by the data cutoff date (29 January 2025), including 111 subjects (43.7%) in the tarlatamab group and 152 subjects (59.6%) in the SOC group. The median (95% CI) follow-up times were 11.2 (10.4, 12.1) months for tarlatamab and 11.7 (10.6, 12.3) months for SOC chemotherapy. The median OS was 13.6 months (95% CI: 11.1, NE) months in the tarlatamab group and 8.3 months (95% CI: 7.0, 10.2) months in the SOC group. The hazard ratio for OS of tarlatamab versus SOC was 0.599 (95% CI: 0.468, 0.768). The 1-sided p-value for OS from the stratified log rank test was < 0.001, which crosses the prespecified interim efficacy boundary of 0.01 and is statistically significant. The Kaplan-Meier estimated OS rates for tarlatamab and SOC, respectively, were 75.6%

(69.8, 80.4) and 61.5% (55.2, 67.1) at 6 months, and 53.4% (46.0, 60.2) and 36.9% (30.3, 43.5) at 12 months. Results from the sensitivity analysis of OS were consistent with the main OS results: analysis using actual strata instead of planned strata (HR 0.609, 95% CI: 0.476, 0.780; $p < 0.001$).

Results from the subgroup analyses of OS were generally consistent with that of the primary analysis in favor of tarlatamab. Additional post hoc subgroup analysis demonstrated the OS benefit of tarlaramab vs chemotherapy regardless of the type of chemotherapy administered (amrubicin, topotecan, or lurbinectedin).

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Table 12. Applicant - Primary Analysis of Overall Survival (ITT Analysis Set)

	Standard of Care (N = 255)	Tarlatamab (N = 254)	Treatment Difference
Subject status			
Events - n (%)			
Death	152 (59.6)	111 (43.7)	
Censored - n (%)	103 (40.4)	143 (56.3)	
Alive at last follow-up	102 (40.0)	143 (56.3)	
Withdrawal of consent from study	1 (0.4)	0 (0.0)	
Decision by sponsor	0 (0.0)	0 (0.0)	
Lost to follow-up	0 (0.0)	0 (0.0)	
Completed study without death	0 (0.0)	0 (0.0)	
Hazard ratio (95% CI)[a]			0.599 (0.468, 0.768)
P-value (1-sided)[b]			< 0.001
P-value (2-sided)[b]			< 0.001
Overall survival (KM) (months)[c]			
25th percentile (95% CI)	4.1 (3.3, 5.0)	6.3 (4.2, 7.9)	
Median (95% CI)	8.3 (7.0, 10.2)	13.6 (11.1, NE)	
75th percentile (95% CI)	NE (16.1, NE)	NE (17.1, NE)	
Min, Max (+ for censored)	0.1, 18.5+	0.1, 17.4+	
Follow-up time for OS (KM) (months)[c]			
25th percentile (95% CI)	9.4 (8.7, 9.9)	9.3 (8.7, 9.8)	
Median (95% CI)	11.7 (10.6, 12.3)	11.2 (10.4, 12.1)	
75th percentile (95% CI)	13.8 (12.7, 14.3)	13.9 (13.1, 14.5)	
Min, Max (+ for censored)	0.1+, 18.5	0.1+, 17.4	
Kaplan-Meier estimate (%) (95% CI)[d]			
At 6 months	61.5 (55.2, 67.1)	75.6 (69.8, 80.4)	
At 12 months	36.9 (30.3, 43.5)	53.4 (46.0, 60.2)	
At 18 months	27.2 (15.2, 40.8)	NE (NE, NE)	

IVRS = interactive voice response system; N = Number of subjects in the analysis set; n = Number of subjects with observed data; NE = not estimable

The follow-up time is measured by reversing the status indicator for censored and events. The randomization stratification factors used in stratified analysis includes chemotherapy-free interval (<90 days, ≥90 days), and presence (previous or current) of brain metastases (yes or no). This stratified analysis is based on IVRS data

[a] Hazard ratios and 95% CIs are estimated using a stratified Cox proportional hazards model; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm

[b] P-value is calculated using a stratified log-rank test

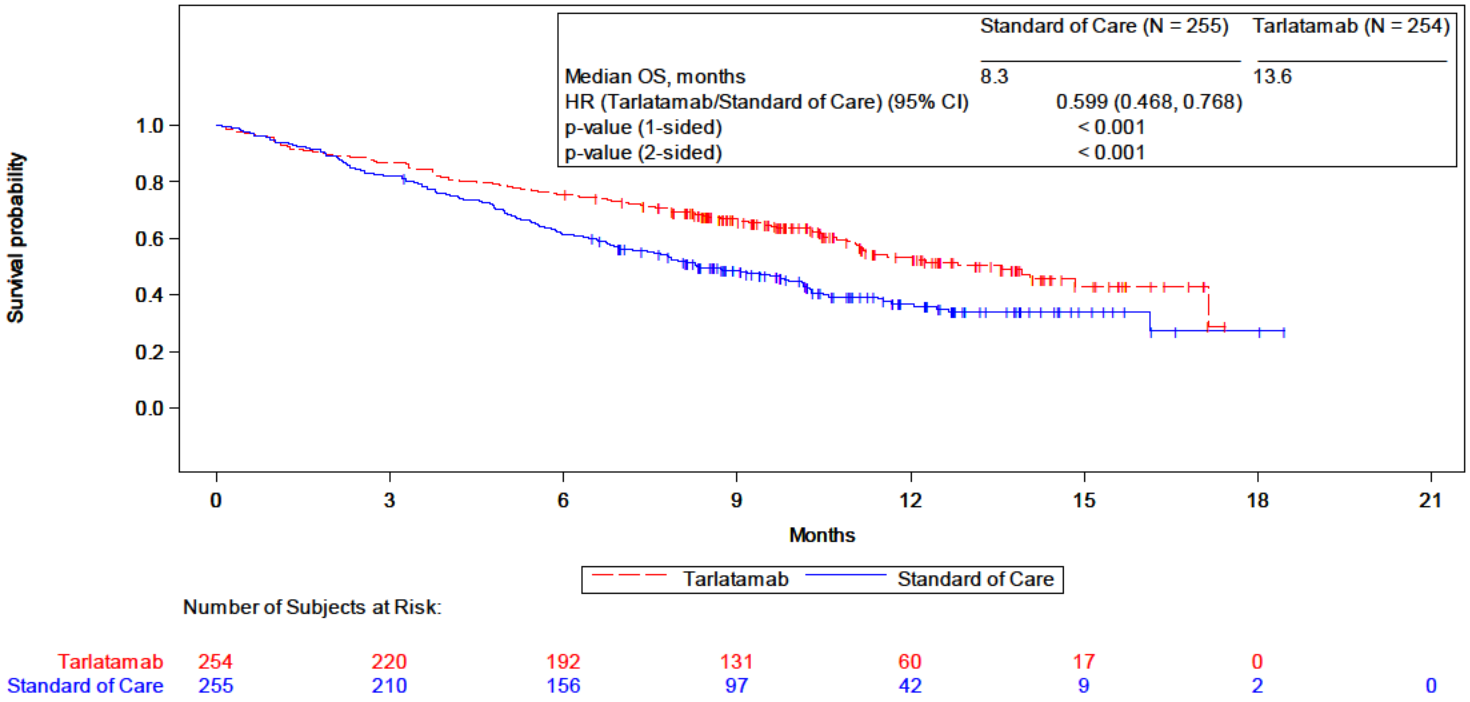
[c] Median and quantiles are estimated using Kaplan-Meier method and 95% CI of median are estimated using log-log transformation of KM survival estimate by Brookmeyer and Crowley (1982) method

[d] 95% CIs are estimated using Kalbfleisch and Prentice (1980) method

Data snapshot date: 13 March 2025; Data cutoff date: 29 January 2025

Source: Table 14-4.1.1 of Study 20210004

Figure 2. Applicant - Kaplan-Meier Plot for Overall Survival (ITT Analysis Set)



IVRS = interactive voice response system; N = Number of subjects in the analysis set
Censor indicated by vertical bar |
The survival curves and median overall survival are estimated using Kaplan-Meier method
Hazard ratio and 95% CI are estimated using a stratified Cox proportional hazards model; a hazard ratio < 1.0 indicates a better survival of tarlatamab arm
This stratified analysis is based on IVRS data
P-value is calculated using a stratified log-rank test
Data snapshot date: 13 March 2025; Data cutoff date: 29 January 2025
Source: Figure 14-4.2.3 of Study 20210004

The Applicant's Position:

Tarlatamab demonstrated a statistically significant and clinically meaningful OS benefit (median OS 13.6 months vs 8.3 months, HR = 0.599 [95% CI: 0.468, 0.768], p-value <0.001) with a 40.1% reduced hazard of death compared with the SOC chemotherapy for the treatment of individuals with SCLC who have progressed on or after platinum-based chemotherapy. Overall survival benefits were generally consistent in favor of tarlatamab across subgroups. However, subgroup analysis interpretation may be limited in certain subgroups because of small sample size.

The FDA's Assessment:

FDA agrees with the Applicant's position that DeLLphi-304 met its primary endpoint of OS. Statistical significance was observed at the first interim analysis of OS which was conducted when 263 events were observed, corresponding to an information fraction (IF) of 76%. An improvement in median OS of 5.3 months was observed with median OS of 13.6 months (95% CI: 11.1, NE) in the tarlatamab arm vs. 8.3 (95% CI: 7.0, 10.2) months in the SOC arm. The HR estimate was 0.60 (95% CI: 0.47, 0.77), with $p < 0.001$ based on a stratified log-rank test.

Given that the median follow up was lower than the median OS estimate of the tarlatamab arm, which was estimated around the timing of the last observed event, FDA requested an updated OS analysis with the 90-day safety update (DCO 4/29/2025). With an additional 3 months of follow-up, at 87% IF, the HR estimate was 0.58 (95% CI: 0.46, 0.73) and median OS estimates were consistent with those at the OS IA: 13.6 months (95% CI: 11.9, NE) for tarlatamab and 8.4 months (95% CI: 7.2, 10.2) for SOC.

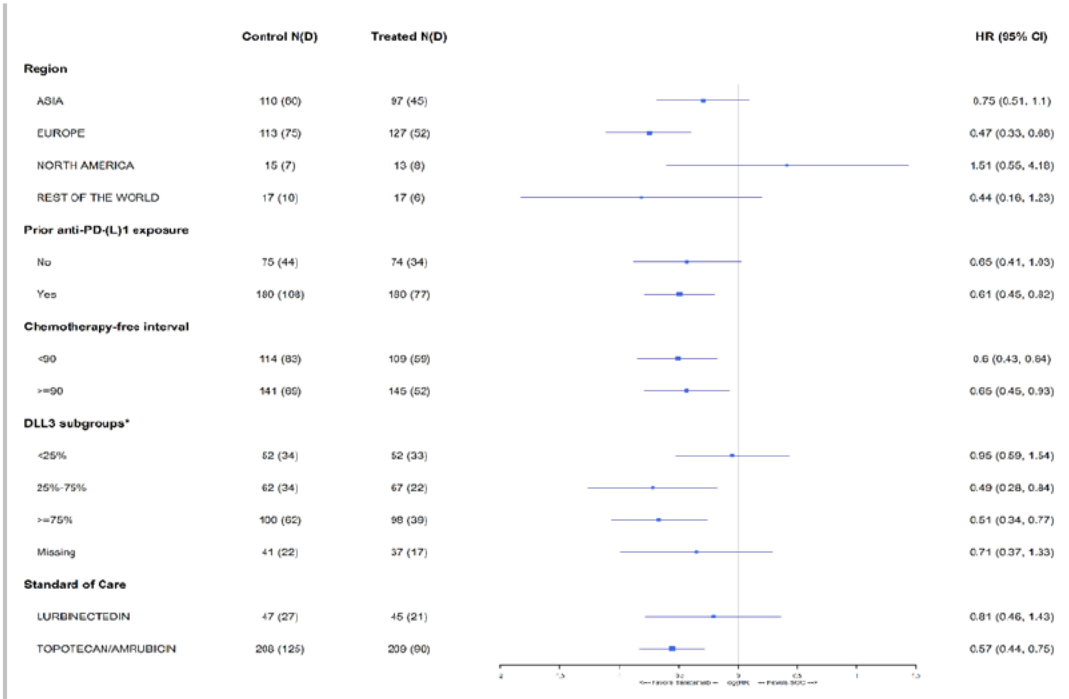
While FDA agrees with the Applicant that the same OS trend favoring the tarlatamab arm was observed regardless of choice of control, the efficacy result appeared to be mainly attributable to the comparative results between tarlatamab and topotecan. The median OS among patients receiving topotecan was 7.5 months (95% CI: 6.3, 9.1), which was considerably shorter than that for patients receiving amrubicin (11.5 months, 95% CI: 6.18, NE) or lurbinectedin (10.6 months, 95% CI: 8.7, NE) in DeLLphi-304, acknowledging the small sample sizes in these groups. Nonetheless, the hazard ratio between tarlatamab and any of the three SOC choices favors tarlatamab. Furthermore, amirubicin is not an approved therapy for SCLC in the U.S. and lurbinectedin is currently under accelerated approval for the indication under study; therefore, topotecan is an appropriate comparator when considering applicability to the U.S. patient population..

Treatment benefit in OS was generally consistent across most other key subgroups with HR estimates below 1, including by prior anti-PD-(L)1 exposure

and chemotherapy free interval (Figure 3). As previously noted the distribution of sex in the trial does not align with the known distribution of sex for SCLC in the U.S.; however, the OS HR was in favor of tarlatamab for both male patients (HR 0.7) and female patients (HR 0.43). Heterogeneous results were observed in the subgroup of patients from North America (all patients were from the US except 1 patient from Canada) with a HR of 1.5 (95% CI: 0.55, 4.18). An ad hoc analysis of these 28 patients (13 received tarlatamab, 15 received SOC) showed imbalances across demographics and disease characteristics. Patients who received tarlatamab had a higher median age (71 vs 64), and there was a lower proportion of patients with ECOG PS 0 (15% vs. 47%), as well as a higher proportion of patients with liver metastases (69% vs. 40%) and <25% DLL3 staining (31% vs. 20%). In addition, patients in this subgroup who received tarlatamab had a higher median sum of diameters than patients who received SOC (105 mm vs. 57 mm). Lastly, 7 patients who received SOC received subsequent treatment with tarlatamab. In contrast, the demographics and disease characteristics from the 240 patients randomized in Europe were balanced and the OS HR was 0.47 (95% CI: 0.33, 0.68). FDA attributes the subgroup results for North America to small patient numbers, imbalances in demographics and disease characteristics and receipt of tarlatamab as subsequent therapy in patients who received SOC. In addition, the OS HR results in other regions, including Europe, provide support for the applicability of the OS results in the ITT population to the U.S. population of patients with ES-SCLC.

It was also noted that the OS HR for patients whose tumors had a DLL3 expression <25% was 0.95. However, the OS HR for patients with no DLL3 expression at moderate or strong intensity staining was 0.75 (95% CI: 0.32, 1.78). Acknowledging the small numbers in this analysis, for OS, there does not appear to be a direct correlation with DLL3 expression. However, given the mechanism of action of tarlatamab, it will be important to review these subgroup data in future potential marketing applications for tarlatamab.

Figure 3. FDA - OS Subgroup Analysis in DeLLphi-304



Source: Reviewer generated analysis [adtte.xml; adsl.xml]

Data Quality and Integrity

Data:

See Section 8.2.1.

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that had an effect on the efficacy review.

The FDA's Assessment:

While there were no major issues that impacted data quality and integrity, in order to facilitate FDA review of the data for key secondary PRO-based endpoints, FDA requested resubmission of the ADQS dataset in a format adhering to FDA's PRO Technical Specification Guidance for submission of PRO data. The data quality of the updated ADQS dataset received on 9/10/2025 is acceptable.

Efficacy Results – Secondary and other relevant endpoints

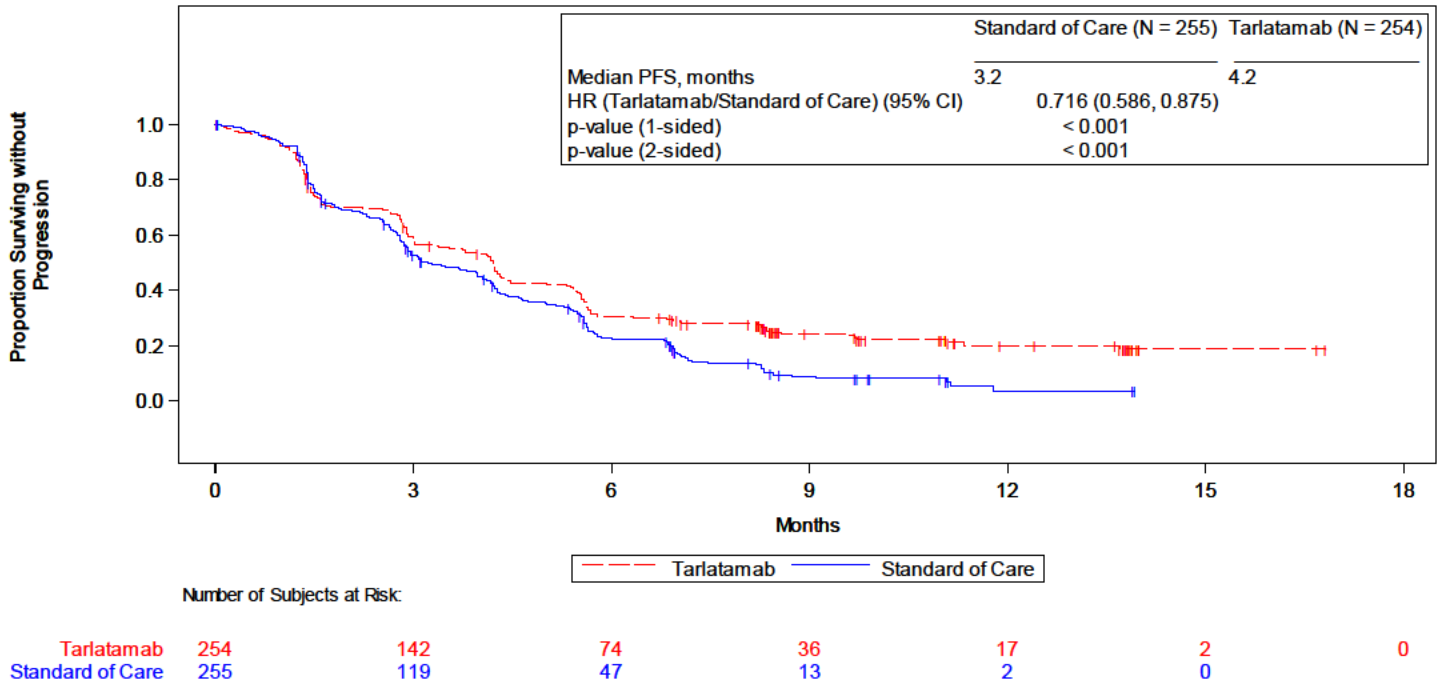
Data:

The PFS and patient reported outcome (PRO) results provide additional evidence of the efficacy of tarlatamab.

PFS: A total of 396 PFS events (191 subjects from the tarlatamab group, 205 subjects from the SOC group) were reported as of the data cutoff. The median PFS as assessed by investigator was 4.2 months (95% CI: 3.0, 4.4) in the tarlatamab group compared with 3.2 months (95% CI: 2.9, 4.2) in the SOC group. The HR for disease progression or death following treatment with tarlatamab vs SOC was 0.716 (95% CI: 0.586, 0.875; p <0.001). The Kaplan-Meier estimated PFS rates were 30.4% (24.8, 36.2) and 22.7% (17.4, 28.4) at 6 months, and 20.1% (14.7, 26.0) and 3.5% (0.9, 9.1) at 12 months for tarlatamab and SOC, respectively (Table 10-3 of Study 20210004). The PFS benefit observed in the tarlatamab group vs the SOC group was consistent across all relevant subgroups. Additional post hoc subgroup analysis demonstrated the PFS benefit of tarlaramab vs chemotherapy regardless of the type of chemotherapy administered (amrubicin, topotecan, or lurbinectedin).

PRO: Tarlatamab demonstrated statistically significant and clinically meaningful reductions in symptom burden related to Dyspnea and Cough. Changes in Chest Pain, Physical Function, and Global Health Status showed a trend toward improvement in favor of tarlatamab. The difference between tarlatamab and SOC chemotherapy in change from baseline after 18 weeks was statistically significant for patient-reported Dyspnea (mean difference −9.14; 95% CI: −12.6, −5.6; p < 0.001) and Cough (odds ratio for improvement 2.0 [95% CI: 1.2, 3.5; p = 0.012]) as measured by Quality of Life Questionnaire 30 (QLQ-C30) and Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13). An improvement trend in Chest Pain was observed, but was not statistically significant (odds ratio for improvement 1.8; 95% CI: 0.9, 3.8; p = 0.100). Due to hierarchical testing strategy, Physical Functioning (least square [LS] mean difference 10.4; 95% CI: 6.0, 14.7) and Global Health Status (LS mean difference 8.9; 95% CI: 5.0, 12.8) were not formally tested, but trended in favor of tarlatamab.

Figure 44. Applicant - Kaplan-Meier Plot for Progression-free Survival as Assessed by Investigator (ITT Analysis Set)



IVRS = interactive voice response system; N = Number of subjects in the analysis set
Censor indicated by vertical bar |
The survival curves and median progression-free survival are estimated using Kaplan-Meier method
Hazard ratio and 95% CI are estimated using a stratified Cox proportional hazards model; a hazard ratio < 1.0 indicates a longer PFS for tarlatamab arm
This stratified analysis is based on IVRS data
P-value is calculated using a stratified log-rank test
Data snapshot date: 13 March 2025; Data cutoff date: 29 January 2025
Source: Figure 14-4.2.2 of Study 20210004.

The Applicant's Position:

The PFS and PRO results provide additional evidence of the efficacy of tarlatamab.

Tarlatamab demonstrated a statistically significant improvement in PFS over SOC chemotherapy. No notable differences were observed among various subgroups for PFS. However, subgroup analysis interpretation may be limited in certain subgroups because of small sample size.

Tarlatamab improved patient-reported outcomes vs SOC chemotherapy. Tarlatamab showed statistically and clinically significant reductions in symptom burden with regards to Dyspnea and Cough. Changes in Chest Pain, Physical Function, and Global Health Status showed a trend toward improvement in favor of tarlatamab.

The FDA's Assessment:

While PFS was statistically significant with a HR estimate of 0.72 (95% CI: 0.59, 0.98) and $p < 0.001$ based on the prespecified stratified log-rank test, the difference in median PFS time was only 1 month with a median PFS of 4.2 months (95% CI: 3.0, 4.4) for patients receiving tarlatamab and 3.2 months (95% CI: 2.9, 4.2) for patients receiving SOC.

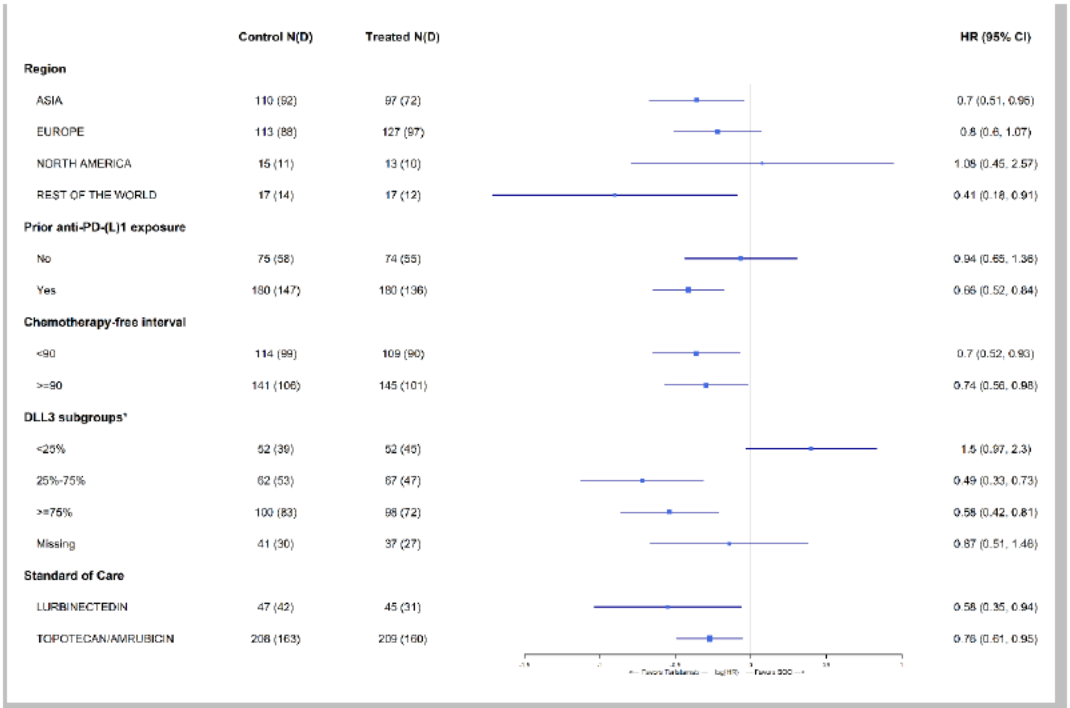
FDA noted that the data on non-target lesion progression did not seem to support progression calls for twelve patients (6 patients from each arm). In response to an FDA IR (9/10/2025), the Applicant stated that investigators determined that the presence of one of the non-target lesion contributed to the overall PD assessment despite SD/PR in target tumor assessments and that this was documented in the SDTM supptr dataset. Sensitivity analyses not including these patients as experiencing events did not materially affect the overall PFS conclusions.

Twenty four patients (21 on the SOC arm and 3 on the tarlatamab arm) received new anti-cancer therapy prior to radiological progression, resulting in censoring of their PFS time at the last adequate tumor assessment prior to receipt of that therapy. Among these 24 patients, 14 patients are listed as having requested the new anti-cancer therapy, while 4 patients experienced an AE.

Treatment benefit in PFS was generally consistent across most key subgroups. However, as with the OS subgroups, heterogeneous results were observed in the subgroup of patients from North America with a HR of 1.08 (95% CI: 0.45, 2.57) and in patients whose tumors had DLL3 expression <25% with a HR of 1.5 (95% CI: 0.97, 2.3). As described in the FDA assessment for OS, there appears to be a plausible explanation for the observations in the North American patient subgroup. For patients whose tumors had no DLL3 expression, the PFS HR was 2.03 (95% CI: 0.95, 4.3) and, therefore, there does appear to be a trend in PFS correlating with lower DLL3 expression. However, given the overall PFS benefit

in this trial was marginal with only a 1 month improvement in median PFS and there does not appear to be a correlation with DLL3 expression and OS, the more meaningful, objective endpoint, FDA does not consider this finding significant enough to warrant any impacts to the label. However, given the mechanism of action of tarlatamab, it will be important to review these subgroup data in future potential marketing applications for tarlatamab. See Figure 5 for FDA's summary of efficacy result by subgroup.

Figure 5. FDA - PFS Subgroup Analysis in DeLLphi-304



Source: Reviewer generated analysis [adtte.xml; adsl.xml]

The tested PRO-based endpoints were derived from the EORTC QLQ-C30 and the EORTC QLQ-LC13 forms which were collected while patients were on study treatment; QLQ-C30 form was expected weekly until week 13 thereafter every 6 weeks, while the QLQ-LC13 form was expected every 6 weeks. After treatment discontinuation, both forms were collected twice more: once at the End of Treatment visit within 14 days of treatment discontinuation and once at the safety follow-up visit within 60 days of treatment discontinuation.

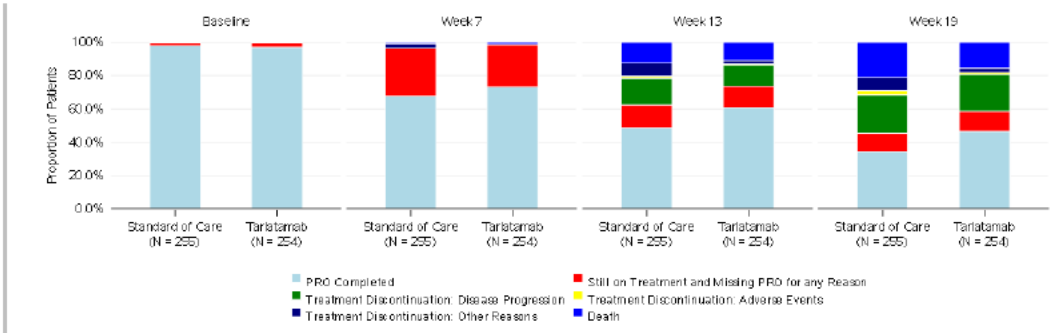
Dyspnea, global health status and physical functioning were multi-item composite scores. Change from baseline through week 18 (measured at week 19) for these scores were tested using a mixed model for repeated measures (MMRM). Cough and chest pain were single-item ordinal outcomes and change from baseline after 18 weeks for these scores was analyzed using Generalized Linear Mixed Model

(GLMM) with cumulative logit link. The analysis population for all PRO-based endpoints was the ITT population. Data collected after treatment discontinuation were not included in the main analysis.

Per the SAP multiplicity plan, dyspnea, cough and chest pain were tested first using Holm's procedure. Dyspnea and cough achieved statistical significance while chest pain did not, halting all further statistical testing of PRO endpoints.

At week 19, 149 patients (59%) randomized to the tarlatamab arm and 116 (45%) patients randomized to the SOC arm were still on treatment. The compliance rates at Week 19 were 79% and 76% respectively; notably the available data rates were 46% and 35% (See Figure 6). In response to an IR (9/10/2025), the Applicant provided a comparison of baseline disease characteristics of patients who completed PRO assessments at Week 19 and the ITT population; notably this subgroup of patients had less disease burden at baseline as measured by sum of diameter of target lesions.

Figure 6. FDA - Available Data Rates for Dyspnea scale (EORTC QLQ-C30 and QLQ-LC13) through Week 18, DeLLphi-304



N = Number of subjects in the randomized population.
Dyspnea composite score represents the composite score of item # 3, 4, and 5 from QLQ-LC13 and item # 8 from QLQ-C30 questionnaires.
Percentage is calculated using randomized population, N.
Data snapshot date: 13MAR2025; Data cutoff date: 29JAN2025.

Source: Response to IR (9/10/2025), page 128

Both MMRM and GLMM models assume missing at random (MAR), meaning the models assume that patients who died (15% on tarlatamab vs. 21% on SOC), or discontinued treatment due to disease progression (22% on tarlatamab vs. 23% on SOC), AE (1% on tarlatamab vs. 2% on SOC), or any other reason (3% on tarlatamab vs. 8% on SOC), which in total accounts for 60% of the analysis population at week 19, will benefit in a similar manner as patients who were still alive and on treatment. Such an assumption is often unrealistic and hard to verify, potentially leading to biased treatment effect estimates.

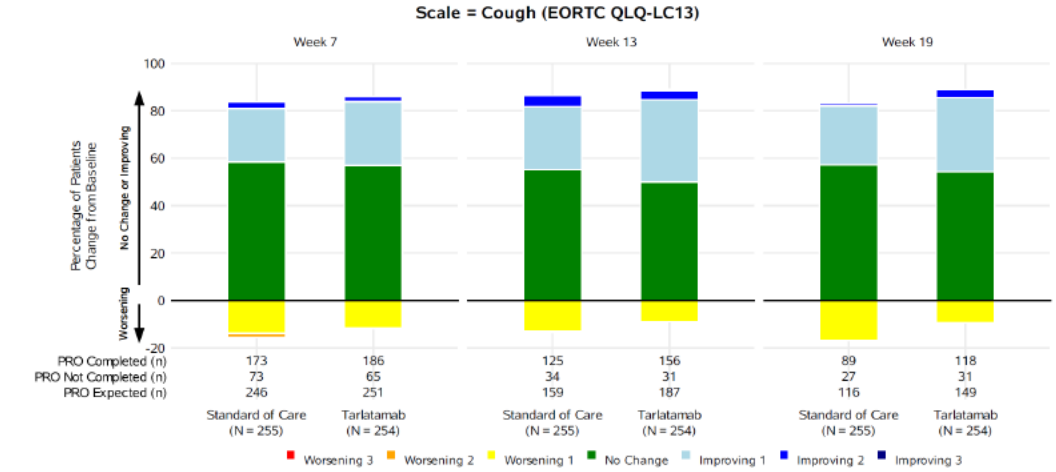
To investigate the effect of the missing data on the treatment effect estimates for cough and dyspnea, the Applicant conducted sensitivity analyses per FDA's request using tipping point analyses and supplementary analyses incorporating

treatment policy strategy for treatment discontinuation (i.e., including data collected up to safety follow-up visit). FDA conducted additional sensitivity analyses based on reference based imputation, which impute missing outcome data based on the SOC arm. The assessment of the two statistically significant PRO endpoints are presented below.

Change from Baseline through Week 18 in Cough

Cough is measured on a 4-point scale (not at all, a little, quite a bit, very much) in the QLQ-LC13 instrument. At baseline, 34% on the tarlatamab arm and 31% on the SOC arm reported no cough, while 52% and 55% respectively reported a little cough. Figure 7 shows the distribution of change in cough from baseline through week 18.

Figure 7. FDA - Distribution of Change in Cough from Baseline through Week 18, DeLLphi-304



Source: Response to IR received on 9/10/2025.

Eighty-nine (35%) patients from the SOC arm and 118 (46%) patients in the tarlatamab arm were still on treatment and completed the PRO assessment and were included in the week 19 analysis. The majority (57% and 55% respectively) of these patients experienced no change in cough, 23 (26% for SOC) and 41 (35% for tarlatamab) of these patients reported improving cough, corresponding to 9% (SOC) and 16% (tarlatamab) in the ITT population. While the result from the GLMM model was statistically significant, with the odds of improvement by one category in cough for patients receiving tarlatamab compared to SOC being 2.04 (95% CI: 1.17, 3.35), given the high percentage of patients with little or no cough at baseline and the large percentage with no change from baseline through week 18, the clinical meaningfulness of these results was not strong despite a statistically significant result. (b) (4)

Change from Baseline through Week 18 in Dyspnea

After 18 weeks, the mean difference of change from baseline in dyspnea between the tarlatamab arm and the SOC arm was -9.14 (95% CI: -12.64, 5.64) based on the MMRM model. To investigate the effect of the substantial amount of missing data on the treatment effect estimates for dyspnea, the Applicant conducted sensitivity analyses per FDA's request using tipping point analyses and incorporating the treatment policy strategy for treatment discontinuation (i.e., including data collected up to safety follow-up visit).

The Applicant performed two tipping point analyses to determine the average Dyspnea score worsening that was needed in the tarlatamab arm to "tip" the results to losing statistical significance. When missing data in the SOC arm were imputed with no change (MAR) and 2-point worsening, respectively, the results indicated that loss of statistical significance occurred when patients in the tarlatamab arm with missing data were assumed to have an average 16-point and 19-point worsening. These are considered unlikely clinical scenarios. When incorporating treatment policy estimand the treatment effect estimate at week 18 decreases to -6.19 (95% CI: -8.88, -3.49).

FDA conducted additional sensitivity analyses using reference based imputation. A "Jump to Reference" sensitivy analysis assumes that once tarlaramab patients have missing dyspnea scores, their scores will immediately "jump" to behave similar to SOC patients. A"Copy Reference" sensitivity analysis assumes tarlatamab patients behave similar to SOC arm patients throughout the entire 18-week span if they missed PRO assessment at any point before week 19. A "Copy Increments in Reference" sensitivity analysis copies the visit-to-visit change patterns (increments) from SOC patients for tarlatmab patients who miss PRO assessment. The sensitivity analyses using reference based imputation also assumes SOC patients who missed PRO assessments behaved the same as other SOC patients with available data at a specific visit, which is potentially unrealistic. Applying any penalty when imputing the missing data for SOC arm patients will further negatively affect the treatment effect estimates. It is observed that statistical significance at week 19 was preserved under all sensitivity analysis scenarios.

The results of the reference based imputation analyses are shown in Table 13**.**

Table 13. FDA - Reference Based Multiple Imputation Analysis of Change From Baseline Through Week 18 for Dyspnea (EORTC QLQ-C30, EORTC QLQ-LC13) (ITT Analysis Set)

Imputation Method	Visit	SOC LS Mean (SE)	Tarlatamab LS Mean (SE)	Difference of LS Means (95% CI)
Jump to reference	Week 7	2.17 (1.21)	-1.83 (1.07)	-4.00 (-6.95, -1.04)
	Week 13	0.97 (1.44)	-3.29 (1.09)	-4.25 (-7.68, -0.83)
	Week 19	6.50 (1.81)	1.40 (1.99)	-5.09 (-8.43, -1.76)
Copy Reference	Week 7	2.17 (1.21)	-1.83 (1.07)	-4.00 (-6.95, -1.04)
	Week 13	0.97 (1.44)	-3.61 (1.11)	-4.57 (-8.08, -1.07)
	Week 19	6.50 (1.81)	0.48 (2.02)	-6.02 (-9.44, -2.61)
Copy Increments in Reference	Week 7	2.17 (1.21)	-1.83 (1.07)	-4.00 (-6.95, -1.04)
	Week 13	0.97 (1.44)	-4.03 (1.11)	-5.00 (-8.58, -1.42)
	Week 19	6.50 (1.81)	-0.49 (1.91)	-7.00 (-10.38, -3.61)

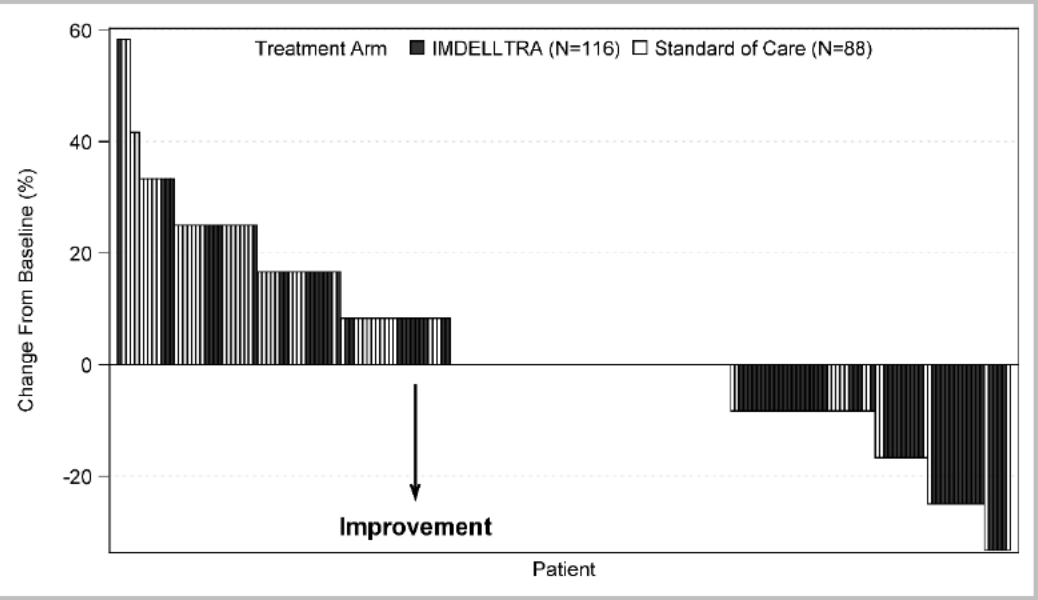
Source: FDA Reviewer generated [adqs.xpt; adsl.xpt];

The difference of mean change from baseline through the end of week 18 ranged from -5.09 to -9.14 based on a variety of modeling assumptions as already discussed. It is noted that all assumptions are strong and unverifiable. While statistical significance is demonstrated for all group level mean differences, obtaining a reliable representation of the treatment effect estimate is challenging due to missing data.

There is no widely used standard of improvement in dyspnea in this disease setting; therefore, it is difficult to determine a specific threshold of clinical meaningfulness. FDA performed exploratory analyses based on the applicants hypothesized -16 point threshold, which showed that among those who completed the PRO assessment at the end of 18 weeks, more patients in the tarlatamab arm (22%) had an improvement in dyspnea compared to the SOC arm (7%).

Figure 8 shows the waterfall plot of change from baseline for Dyspnea at week 18 for all patients with both baseline and week 18 PRO assessments. From the waterfall plot, the majority of the patients showing improved dyspnea received tarlatamab while more patients on the SOC arm showed worse dyspnea; 33% patients in the tarlatamab arm and 30% patients in the SOC arm reported no change in dyspnea at all.

Figure 8. FDA - Waterfall Plot of Change from Baseline for Dyspnea (EORTC QLQ-C30, EORTC QLQ-LC13) through Week 18



Source: FDA Reviewer generated [adqs.xpt]

Overall, a change from baseline through Week 18 in patient-reported dyspnea was pre-specified in the multiplicity plan with Type I error control. The endpoint was statistically significant, and statistical significance was shown to be robust based on a variety of sensitivity analyses, including tipping point analyses, conducted by both the Applicant and FDA. However, the estimation of the treatment effect remains uncertain given the amount and reasons for missing data which includes death, disease progression, and discontinuation due to AE. Based on the experience of patients on treatment who responded to the dyspnea scale, FDA supports including a statement in in Section 14 of the product label indicating that the analysis of mean change from baseline in dyspnea at week 18 demonstrated a statistically significant improvement in patients randomized to tarlatamab compared to SOC, while only including data in the label which describes tarlatamab's treatment benefit in patient-reported dyspnea compared to SOC descriptively.

Dose/Dose Response

Data:

See Section 6.3.2, Clinical Pharmacology Questions.

The Applicant's Position:

The proposed dose of 10 mg Q2W is effective and generally well tolerated in subjects with advanced SCLC. The proposed dosing regimen is supported by the observed efficacy and safety-data and demonstrates a favorable benefit-risk profile. Overall, results of exposure-response analysis for efficacy measures suggest the proposed dosing regimen of 10 mg Q2W exhibited near maximal efficacy in the intended patient population, and exposures associated with lower doses are estimated to have lower efficacy. None of the covariates evaluated in the exposure-response analysis resulted in clinically meaningful changes in efficacy and therefore do not warrant a dose adjustment.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the labeled dosing regimen demonstrates a favorable benefit-risk profile and is appropriate as the recommended dosage of tarlatamab for the indication under review.

Durability of Response

Data:

The ORR was 35.0% (95% CI: 29.2, 41.3) in the tarlatamab group versus 20.4% (95% CI: 15.6, 25.9) in the SOC group (odds ratio of 2.1; 95% CI: 1.4, 3.2).

As of data cutoff, 42 subjects (47.2%) in the tarlatamab group and 8 subjects (15.4%) in the SOC chemotherapy group were having an ongoing response. Eighty-nine subjects in the tarlatamab group and 52 subjects in the SOC chemotherapy group had a confirmed best overall response of complete response or partial response. The median (95% CI) follow-up times were 9.7 (6.9, 11.1) months for tarlatamab and 8.3 (7.1, 9.7) months for SOC chemotherapy. The median (95% CI) DOR for the 89 responses in the tarlatamab group was 6.9 (4.5, 12.4) months, with a median (range) time to response of 1.5 (1.2, 6.9) months. The median (95% CI) DOR for the 52 responses in the SOC chemotherapy group was 5.5 (4.2, 5.7) months, with a median (range) time to response of 1.4 (1.2, 5.4) months.

The Applicant's Position:

Higher ORR and longer DOR results in the tarlatamab group compared with the SOC chemotherapy group further support the durable clinical benefit of tarlatamab in this patient population with high unmet medical need.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of descriptive endpoints ORR and DOR. In addition, based on observed duration of response (not Kaplan-Meier estimates), 46% of responders on the tarlatamab arm had a DOR of 6 months or longer and 13% had DOR lasting 12 months or longer.

Persistence of Effect

Data:

No long-term efficacy data with the exception of those presented in the preceding sections are available at the time of this application.

The Applicant's Position:

Not Applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

See Efficacy Results – Secondary and other relevant endpoints for data.

The Applicant's Position:
See Efficacy Results – Secondary and other relevant endpoints for data.

The FDA's Assessment:

FDA agrees with the Applicant's position. Please see FDA assessment in the secondary and other relevant endpoints section.

Additional Analyses Conducted on the Individual Trial

Data:

Not Applicable.

The Applicant's Position:

Not Applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

The review of effectiveness for this application was based on the efficacy analyses conducted in the ITT population of the tarlatamab monotherapy and SOC arms of the DeLLphi-304 study. These analyses included 509 patients and are based on results from the first planned interim analysis (DCO: January 29, 2025), corresponding to an information fraction of 76% for OS.

The study met its primary endpoint of OS, demonstrating a statistically significant and clinically meaningful improvement with a HR of 0.60 ([95% CI: 0.47, 0.77], p<0.001) for OS, corresponding to a median OS of 13.6 months (95% CI: 11.1, NE) in the tarlatamab arm and 8.3 months (95% CI: 7, 10.2) in the SOC arm. The survival benefit was consistent across the majority of subgroups. The exceptions to this is the subgroup of patients who were from North America and those whose tumors had DLL3 expression <25%.

For the subgroup of patients who were from North America, ad hoc analysis showed some notable differences in baseline characteristics; specifically, patients who received tarlatamab compared to SOC in this subgroup were older, and there was a higher proportion of patients with an ECOG PS of 1, a higher burden of disease in terms of higher median sum of diameters of target lesions, and higher proportion of patients with liver metastases. In addition, 7 of the 13 patients in the SOC arm received subsequent tarlatamab. This suggests that imbalances between arms in higher risk characteristics in this small subgroup of patients along with patients in the SOC arm who received subsequent tarlatamab may have contributed to the observed HR for OS. In addition, the OS HR results in other regions, including Europe, provide support for the applicability of the OS results in the ITT population to the U.S. population of patients with ES-SCLC. Regarding DLL expression, there did not appear to be a direct correlation between DLL3 expression and OS improvement as patients whose tumors had no DLL3 expression had a more favorable OS HR point estimate compared to the DLL3 expression <25% subgroup.

For the key secondary endpoints, the study met its endpoint of investigator assessed PFS, demonstrating a statistically significant improvement (p < 0.001) with a HR of 0.72 (95% CI: 0.59, 0.88) corresponding to a median PFS of 4.2 months (95% CI: 3, 4.4) in the tarlatamab arm compared to 3.2 months (95% CI: 2.9, 4.2) in the SOC arm. The study also met its PRO-based endpoints of dyspnea and cough, demonstrating statistically significant improvements in these two PRO-based

measures. Although the cough results were statistically significant, given the proportion of patients who had cough at baseline and the odds ratio result, FDA considered this result less clinically meaningful. While the dyspnea results were both statistically significant and clinically meaningful, estimation of the treatment effect remains uncertain; thus FDA supported a descriptive approach to labeling.

Overall, these results from DeLLphi-304 provide substantial evidence of effectiveness for tarlatamab for the treatment of patients with ES-SCLC with disease progression on or after platinum-based chemotherapy.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

See Efficacy Results – Primary Endpoint (including Sensitivity Analyses).

The Applicant's Position:

The primary evidence for the efficacy for this marketing application is evaluation of data of tarlatamab compared with SOC for the treatment of subjects with relapsed SCLC after platinum-based first-line chemotherapy in the pivotal phase 3 Study 20210004, as demonstrated by a statistically significant and clinically meaningful OS benefit compared with the SOC chemotherapy.

The efficacy results from the subjects with third-line or later SCLC enrolled in phase 2 Study 20200491 and subjects with advanced SCLC enrolled in FIH Study 20160323 provide supportive efficacy data.

The FDA's Assessment:

FDA agrees with the Applicant's position. Please see the integrated review of effectiveness section on FDA's assessment on DeLLphi-304 (Study 20210004). The efficacy results from the Study 20200491 (DeLLphi-301), which supported the accelerated approval of tarlatamab for the same indication currently under review for traditional approval, are considered supportive efficacy data.

Secondary and Other Endpoints

Data:

See Efficacy Results – Secondary and other relevant endpoints.

The Applicant's Position:

Tarlatamab demonstrated a statistically significant and clinically meaningful benefit for the key secondary endpoint of PFS (median PFS 4.2 months vs 3.2 months, HR = 0.716 ([95% CI: 0.586, 0.875], p-value <0.001), resulting in a 28.4% reduced hazard of disease progression or death compared with the SOC chemotherapy. Higher ORR and longer DOR results in the tarlatamab group compared with the SOC chemotherapy group further support the durable clinical benefit of tarlatamab in this patient population with high unmet medical need.

The FDA's Assessment:

The PFS data provided above is not relevant to this section as it is limited to data from DeLLphi-304. While only descriptive data, ORR with tarlatamab in DeLLphi-304 and DeLLphi-301 were similar, demonstrating consistency across trials.

Subpopulations

Data:

Analyses for OS, PFS and ORR in Study 20210004 were conducted to explore the consistency of tarlatamab treatment effect across subgroups of age, sex, race, region, prior PD-1 or PD-L1 therapy, chemotherapy-free interval, brain metastasis at baseline, SOC and DLL3 cut points. Additional post hoc subgroup analysis demonstrated the OS, PFS and ORR benefit of tarlaramab vs SOC chemotherapy regardless of the type of chemotherapy administered (amrubicin, topotecan, or lurbinectedin).

The Applicant's Position:

No notable differences were observed among these subgroups for OS, PFS, or ORR. However, subgroup analysis interpretation in certain subgroups may be limited because of small sample size.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. As discussed in previous sections, heterogeneous results were observed in the subgroup of patients from North America (all patients were from the US except 1 patient from Canada) with an OS HR of 1.5 (95% CI: 0.55, 4.18). An adhoc analysis of these 28 patients (13 received tarlatamab, 15 received SOC) showed imbalances across demographics and disease characteristics. Patients who received tarlatamab had a higher median age (71 vs 64), a lower proportion of patients with ECOG PS 0 (15% vs. 47%), as well as a higher proportion of patients with liver metastases (69% vs. 40%), and <25% DLL3 staining (31% vs. 20%). In addition, patients who received tarlatamab had a higher median sum of diameters than patients who received SOC (105 mm vs. 57 mm). Lastly, 7 patients who received SOC received subsequent

tarlatamab. In contrast, the demographics and disease characteristics from the 240 patients randomized in Europe were balanced and the OS HR was 0.47 (95% CI: 0.33, 0.68). FDA cannot rule out that the subgroup results may be attributed to small patient numbers, imbalances in demographics and disease characteristics and receipt of tarlatamab as subsequent therapy in patients who received SOC. The OS HR results in other regions, including Europe, provide support for the applicability of the OS results in the ITT population to the U.S. population of patients with ES-SCLC.

It was also noted that the OS HR for patients whose tumors had a DLL3 expression <25% was 0.95 (95% CI: 0.59, 1.54). However, the OS HR for patients with no DLL3 expression at moderate or strong intensity staining was 0.75 (95% CI: 0.32, 1.78). While there does not appear to be a direct correlation with DLL3 expression for OS, given the mechanism of action of tarlatamab, it will be important to review these subgroup data in future potential marketing applications for tarlatamab.

Given that DeLLphi-301 did not randomize patients between tarlatamab and SOC, ORR is the only appropriate endpoint to consider for subgroup analyses; however, it is not possible to interpret results for the North American subgroup of patients, as only 3 patients in DeLLphi-301 were from North America. Regarding DLL3 expression, review of DeLLphi-301 efficacy data at validated cutoffs did not show any differences in ORR across subgroups; there were also 2 patients with DLL3-negative SCLC, with one patient having a response to tarlatamab.

Only 1% of patients in the overall study population were Black/African American. Similar to representation in the DeLLphi-300 and DeLLphi-301 studies, this underrepresents the proportion of Black/African American patients in the U.S., who comprise about 9% of the U.S. patient population with SCLC (SEER database). A PMC was issued at the time of the initial approval of tarlatamab for an integrated analysis from ongoing, completed, or planned clinical trials and other potential data sources as appropriate enrolling a sufficient representation of U.S. racial and ethnic minority patients that is reflective of the U.S. population of patients with SCLC, to further characterize the efficacy, safety and pharmacokinetics of tarlatamab in these patients, and this PMC remains open.

Additional Efficacy Considerations

The FDA's Assessment:

No additional efficacy analyses were conducted.

8.1.5. Integrated Assessment of Effectiveness

Data:

Data are presented above in Section 8.1.2. Efficacy data were not pooled across the phase 1, 2, and 3 studies due to differences in study design (active comparator vs no comparator), number of prior cancer treatments (≥ 1, 1+, or ≥ 2+), and tarlatamab dose.

The Applicant's Position:

Results from Study 20210004 demonstrated the clinical activity of tarlatamab in subjects with advanced SCLC, a disease state with high unmet medical need.

Overall, tarlatamab demonstrated a statistically significant and clinically meaningful improvement in OS and PFS over SOC. Overall survival benefits and PFS were generally consistent across key subgroups in favor of tarlatamab. Patients treated with tarlatamab have improved patient-reported outcomes compared to SOC. Tarlatamab demonstrated statistically significant and clinically meaningful reductions in symptom burden related to Dyspnea and Cough. Changes in Chest Pain, Physical Function, and Global Health Status showed a trend toward improvement in favor of tarlatamab.

The FDA's Assessment:

This sBLA is primarily supported by results from DeLLphi-304, a multicenter, international, open-label, randomized trial in patients with ES-SCLC whose disease has progressed after one prior platinum-containing regimen. Please see the Integrated Review of Effectiveness section for FDA's detailed assessment of results from DeLLphi-304 (Study 20210004).

The submitted evidence meets the statutory evidentiary standard for traditional approval of tarlatamab for the treatment of adult patients with ES-SCLC with disease progression on or after platinum-based chemotherapy. The observed statistically significant improvement in OS with a HR of 0.60, corresponding to a 5.3-month difference in median OS, is clinically meaningful and represents a major improvement for patients with ES-SCLC. The positive OS results are supported by a statistically significant benefit in PFS, as well as a higher ORR in the tarlatamab arm vs the SOC arm. In addition, the PRO endpoint of mean change from baseline in dyspnea as assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 at week 18 demonstrated a statistically significant improvement in patients randomized to tarlatamab compared to SOC. The original data supporting the accelerated approval of tarlatamab provide supportive evidence of the effectiveness of tarlatamab in the indicated population.

Overall, these results provide substantial evidence of effectiveness and support a recommendation for the traditional approval of tarlatamab for the following

indication: *treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy*.

8.2. **Review of Safety**

Data:

As of the time of this marketing application, the number of subjects who have been exposed to ≥ 1 dose of tarlatamab is provided in Table 10.

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Table 14: Applicant – Exposure to Tarlatamab – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Number of doses per participant				
n	252	0	473	730
Mean	13.3	-	14.6	14.6
SD	9.6	-	13.3	15.4
Median	11.0	-	10.0	9.0
Q1, Q3	5.0, 20.0	-, -	5.0, 20.0	4.0, 19.0
Min, Max	1, 39	-, -	1, 88	1, 98

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The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.
N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.
Study 20210004 Tarlatamab 10 mg includes Study 20210004 1->10 mg. Study 20210004 SOC Chemotherapy includes Study 20210004 amrubicin, lurbinectedin, topotecan. Integrated Analysis Tarlatamab 10 mg includes Study 20210004 1->10 mg; Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); Study 20160323 cohorts 8, 32 and 35. Integrated Analysis Tarlatamab All Doses includes all participants who receive any dose of tarlatamab monotherapy from Studies 20210004, 20200491, and 20160323.
[a] Relative dose intensity (%) is calculated as (actual cumulative dose/planned cumulative dose)*100, where cumulative actual dose is the total dose of tarlatamab given up to the data cutoff. For participants who did not take any drug the cumulative actual dose is 0 mg; Cumulative planned dose is the planned dose of tarlatamab accumulated over the actual duration on study treatment.
Data snapshot date: 06DEC2024 for Study 20160323; 16DEC2024 for Study 20200491; 13MAR2025 for Study 20210004.
Data cutoff date: 18OCT2024 for Studies 20160323 and 20200491; 29JAN2025 for Study 20210004.
Source: ISS Table 14-5.1.400

Table Applicant – Exposure to Tarlatamab – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Cumulative dose (mg)				
n	252	0	473	730
Mean	123.542	-	135.007	478.497
SD	95.368	-	129.096	1164.824
Median	101.000	-	91.000	126.000
Q1, Q3	41.000, 191.000	-, -	41.000, 191.000	41.000, 311.000
Min, Max	1.000, 381.000	-, -	1.000, 671.000	0.036, 9701.000

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The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.
N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.
Study 20210004 Tarlatamab 10 mg includes Study 20210004 1->10 mg. Study 20210004 SOC Chemotherapy includes Study 20210004 amrubicin, lurbinectedin, topotecan. Integrated Analysis Tarlatamab 10 mg includes Study 20210004 1->10 mg; Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); Study 20160323 cohorts 8, 32 and 35. Integrated Analysis Tarlatamab All Doses includes all participants who receive any dose of tarlatamab monotherapy from Studies 20210004, 20200491, and 20160323.
[a] Relative dose intensity (%) is calculated as (actual cumulative dose/planned cumulative dose)*100, where cumulative actual dose is the total dose of tarlatamab given up to the data cutoff. For participants who did not take any drug the cumulative actual dose is 0 mg; Cumulative planned dose is the planned dose of tarlatamab accumulated over the actual duration on study treatment.
Data snapshot date: 06DEC2024 for Study 20160323; 16DEC2024 for Study 20200491; 13MAR2025 for Study 20210004.
Data cutoff date: 18OCT2024 for Studies 20160323 and 20200491; 29JAN2025 for Study 20210004.
Source: ISS Table 14-5.1.400

Table 10. Applicant – Exposure to Tarlatamab – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Relative dose intensity (%)[a]				
n	252	0	473	730
Mean	92.77	-	91.70	89.54
SD	16.14	-	19.73	33.24
Median	100.00	-	100.00	100.00
Q1, Q3	92.91, 100.00	-, -	90.10, 100.00	87.65, 100.00
Min, Max	4.8, 100.0	-, -	3.2, 225.5	0.3, 663.3

The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.
N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.
Study 20210004 Tarlatamab 10 mg includes Study 20210004 1->10 mg. Study 20210004 SOC Chemotherapy includes Study 20210004 amrubicin, lurbinectedin, topotecan. Integrated Analysis Tarlatamab 10 mg includes Study 20210004 1->10 mg; Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); Study 20160323 cohorts 8, 32 and 35. Integrated Analysis Tarlatamab All Doses includes all participants who receive any dose of tarlatamab monotherapy from Studies 20210004, 20200491, and 20160323.
[a] Relative dose intensity (%) is calculated as (actual cumulative dose/planned cumulative dose)*100, where cumulative actual dose is the total dose of tarlatamab given up to the data cutoff. For participants who did not take any drug the cumulative actual dose is 0 mg; Cumulative planned dose is the planned dose of tarlatamab accumulated over the actual duration on study treatment.
Data snapshot date: 06DEC2024 for Study 20160323; 16DEC2024 for Study 20200491; 13MAR2025 for Study 20210004.
Data cutoff date: 18OCT2024 for Studies 20160323 and 20200491; 29JAN2025 for Study 20210004.
Source: ISS Table 14-5.1.400

Table 10. Applicant – Exposure to Tarlatamab – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Treatment duration (weeks)				
n	252	0	473	730
Mean	23.74	-	26.55	27.06
SD	19.36	-	27.30	32.50
Median	18.21	-	18.00	16.14
Q1, Q3	6.14, 37.50	-, -	6.14, 37.57	4.43, 36.43
Min, Max	0.1, 74.6	-, -	0.1, 175.1	0.1, 204.1
Treatment duration (months) - n (%)				
≥ 3	149 (59.1)	0 (0.0)	275 (58.1)	396 (54.2)
≥ 6	104 (41.3)	0 (0.0)	188 (39.7)	266 (36.4)
≥ 9	58 (23.0)	0 (0.0)	114 (24.1)	169 (23.2)
≥ 12	26 (10.3)	0 (0.0)	66 (14.0)	110 (15.1)

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The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.
N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.
Study 20210004 Tarlatamab 10 mg includes Study 20210004 1->10 mg. Study 20210004 SOC Chemotherapy includes Study 20210004 amrubicin, lurbinectedin, topotecan. Integrated Analysis Tarlatamab 10 mg includes Study 20210004 1->10 mg; Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); Study 20160323 cohorts 8, 32 and 35. Integrated Analysis Tarlatamab All Doses includes all participants who receive any dose of tarlatamab monotherapy from Studies 20210004, 20200491, and 20160323.
[a] Relative dose intensity (%) is calculated as (actual cumulative dose/planned cumulative dose)*100, where cumulative actual dose is the total dose of tarlatamab given up to the data cutoff. For participants who did not take any drug the cumulative actual dose is 0 mg; Cumulative planned dose is the planned dose of tarlatamab accumulated over the actual duration on study treatment.

Data snapshot date: 06DEC2024 for Study 20160323; 16DEC2024 for Study 20200491; 13MAR2025 for Study 20210004.
Data cutoff date: 18OCT2024 for Studies 20160323 and 20200491; 29JAN2025 for Study 20210004.
Source: ISS Table 14-5.1.400

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The Applicant's Position:

Data from these studies allow for an informed assessment of the safety profile of tarlatamab and an evaluation of the overall benefit-risk in adult subjects with SCLC with disease progression on or after platinum-based chemotherapy. This population is also considered appropriate for the detection and characterization of common adverse events and to provide guidance on toxicity management.

The FDA's Assessment:

FDA generally agrees with the Applicant's description and pooling of studies. FDA's safety review approach for the proposed indication was based on the 90 day safety update datasets which used a data cutoff date of April 29, 2025. At the updated data cut-off date, among the 252 patients treated with taralatamab in DeLLphi-304, 18% were exposed for greater than 1 year, while among the 473 patients in the pooled safety population, 19% were exposed for greater than 1 year. FDA did not independently review tarlatamab pooled data across all doses as part of their assessment and focused the review on data from patients who received tarlatamab at the labeled dose (10 mg following step up dosing).

8.2.1. Safety Review Approach

Data:

Not Applicable.

The Applicant's Position:

The safety analysis of tarlatamab compared to SOC is primarily supported by data from pivotal phase 3 Study 20210004. The primary integrated safety analysis is based on the integrated safety analysis of pooled data from subjects with SCLC treated with tarlatamab monotherapy at a dose of 10 mg Q2W across Studies 20210004, 20200491 and 20160323; this population is the primary focus in this section. Supportive integrated safety data across all doses and all subjects who received tarlatamab as monotherapy in these studies are provided in Module 2.7.4, Summary of Clinical Safety (SCS) and in the Integated Summary of Safety (ISS). Additional data supporting the proposed safety monitoring period is provided for the following studies:

- Study 20230273, a phase 2a, multicenter, single-arm, open-label study evaluating tarlatamab in Chinese subjects with advanced SCLC after two or more prior lines of treatment (DeLLphi-307) (Section 2.1.6.1.2.2 of Module 2.7.4, SCS).
- Study 20230016, a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of tarlatamab for subjects with limited-stage SCLC who have not progressed after completion of concurrent chemoradiation therapy (DeLLphi-306) (Section 2.1.6.1.2.2 of Module 2.7.4, SCS).
- Study 20200041, a phase 3, randomized, open-label study evaluating the efficacy and safety of tarlatamab plus durvalumab compared with durvalumab alone for

subjects with extensive-stage SCLC with ongoing response or stable disease after completion of first-line therapy with platinum chemotherapy, etoposide, and durvalumab (DeLLphi-305)) (Section 2.1.6.1.2.3 of Module 2.7.4, SCS).

Disposition was summarized using all enrolled subjects; demographics, baseline disease characteristics, exposure, adverse events, and other safety assessments were summarized using the safety analysis set, which included all subjects enrolled who received ≥ 1 dose of tarlatamab.

Throughout the tarlatamab clinical development program, safety was continuously evaluated by Amgen through routine signal detection activities such as review of all serious adverse events across all the clinical studies.

Five adverse events of interest (EOIs) were analyzed for tarlatamab: CRS, neutropenia, ICANS and associated neurological events, neurological events (nervous system disorders [system organ class]/psychiatric disorders [system organ class]), and the potential risk (not important) of hypersensitivity. These events were clinically monitored through protocol designated reporting of clinical signs and symptoms, as well as scheduled assessments of laboratory tests when applicable.

The FDA's Assessment:

FDA agrees with the Applicant's safety review approach and the datasets used for the review of safety results.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

In the tarlatamab group, a total of 252 subjects (99.2%) received at least 1 dose of tarlatamab and are included in the safety analysis set. In the tarlatamab group the median (range) duration of treatment was 18.21 (0.1, 74.6) weeks administered over 5.0 (1, 19) cycles, the median (range) number of investigational product doses received was 11.0 (1, 39), and the median (range) cumulative investigational product dose was 101.00 (1.0, 381.0) mg . In the SOC chemotherapy group, the safety analysis set included 244 subjects. In the SOC chemotherapy group (median [Q1, Q3]), the duration of treatment was 10.9 (3.9, 21.6) weeks administered over 4.0 (2.0, 8.0) cycles, and the cumulative investigational product dose was 24.9 (11.6, 48.6) mg/m^2. In the SOC chemotherapy group the median (range) duration of treatment was 10.86 (0.1, 64.0) weeks administered over 4.0 (1, 21) cycles, the median (range) number of investigational product doses received was 15.0 (1, 105), and the median (range) cumulative investigational product dose was 24.93 (1.4, 2209.6) mg/m^2.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323

A total of 473 of 476 subjects (99.4%) were treated with tarlatamab 10 mg Q2W dose across Studies 20210004, 20200491, and 20160323 (Table 10). The median (range) duration of treatment for tarlatamab monotherapy at 10 mg across Studies 20210004, 20200491 and 20160323 was 18.0 (0.1, 175.1) weeks and the cumulative dose (median [range]) was 91.0 (1.0, 671.0) mg. A total of 372 subjects (78.2%) had discontinued treatment as of the data cutoff date and the most frequently reported (≥10% of subjects) reason for treatment discontinuation was disease progression (62.4%).

The Applicant's Position:

A total of 473 subjects treated with tarlatamab 10 mg Q2W dose across Studies 20210004, 20200491, and 20160323.

The FDA's Assessment:

FDA generally agrees with the Applicant's presentation of exposure and disposition data. The exposure to tarlatamab provided allowed for an adequate assessment of safety. From the updated data provided at the 90 day safety update, among the 473 patients who received tarlatamab at the 10 mg Q2W dose across the DeLLphi-300, DeLLphi-301 and DeLLphi-304, a total of 392 subjects (82%) had discontinued treatment as of the data cutoff date and the most frequently reported (≥10% of patients) reason for treatment discontinuation was disease progression (66%). Among the 473 patients in the pooled safety population, 40% were exposed for 6 months or longer and 19% were exposed for greater than 1 year. Among the 252 patients who received tarlatamab in DeLLphi-304, 41% were exposed for 6 months or longer and 18% were exposed for greater than 1 year.

Relevant characteristics of the safety population:

Data:

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

Of the 509 subjects enrolled in Study 20210004, most were men (69.0%), and were White (57.2%) or Asian (40.1%). Subjects that were White were mostly not Hispanic/Latino (52.7%). The median (range) age was 65 (20 to 86) years. No noteworthy differences in baseline demographics were observed between the tarlatamab and SOC chemotherapy groups (Table 11).

Integrated Safety Analysis of Tarlatamab 10 mg Q2Warm in Studies 20210004, 20200491, and 20160323:

Baseline demographics in subjects treated with tarlatamab 10 mg were comparable to tarlatamab all doses data with respect to sex (67.7% men), race (65.8% White [61.9% not Hispanic or Latino] or 30.9% Asian), and age (median [range]: 65.0 [20 to 86] years). Baseline characteristics in subjects treated with tarlatamab 10 mg were generally consistent with those for the overall population. Subjects had a median (range) of 1.0 (1 to 6) prior lines of therapy, including prior PD-1 or PD-L1 (74.8%). Most subjects had prior radiotherapy (69.8%). Most subjects had metastatic disease (92.6%), including

liver metastases in 37.2% and brain metastasis in 35.1%. Most subjects (67.0%) had an ECOG performance score of 1.

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Table 15. Applicant - Baseline Demographics – Studies 20210004, 20200491, and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Sex - n (%)				
Male	180 (71.4)	161 (66.0)	320 (67.7)	481 (65.9)
Female	72 (28.6)	83 (34.0)	153 (32.3)	249 (34.1)
Race – n (%)				
Asian	96 (38.1)	105 (43.0)	146 (30.9)	201 (27.5)
Black or African American	2 (0.8)	3 (1.2)	6 (1.3)	12 (1.6)
White	151 (59.9)	131 (53.7)	311 (65.8)	492 (67.4)
Ethnicity - n (%)				
Hispanic or Latino	12 (4.8)	11 (4.5)	18 (3.8)	21 (2.9)
Not Hispanic or Latino	139 (55.2)	120 (49.2)	293 (61.9)	471 (64.5)
American Indian or Alaska Native	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.4)	3 (1.2)	8 (1.7)	23 (3.2)
Missing	1 (0.4)	2 (0.8)	1 (0.2)	1 (0.1)

Footnotes are defined on the last page.

Table 11. Applicant - Baseline Demographics – Studies 20210004, 20200491, and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Age (years)				
n	252	244	473	730
Mean	63.6	64.2	63.8	63.1
SD	9.4	9.2	8.9	9.0
Median	64.0	66.0	65.0	64.0
Q1, Q3	58.0, 70.0	58.5, 70.0	58.0, 70.0	58.0, 69.0
Min, Max	20, 86	26, 84	20, 86	20, 86
Age group - n (%)				
18 - 64 years	128 (50.8)	109 (44.7)	233 (49.3)	393 (53.8)
65 - 74 years	95 (37.7)	111 (45.5)	188 (39.7)	272 (37.3)
75 - 84 years	27 (10.7)	24 (9.8)	50 (10.6)	63 (8.6)
≥ 85 years	2 (0.8)	0 (0.0)	2 (0.4)	2 (0.3)
Region – n (%)				
North America	12 (4.8)	14 (5.7)	55 (11.6)	117 (16.0)
Europe	127 (50.4)	107 (43.9)	253 (53.5)	388 (53.2)
Asia	41 (16.3)	57 (23.4)	90 (19.0)	142 (19.5)
Rest of the world	72 (28.6)	66 (27.0)	75 (15.9)	83 (11.4)

The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.
N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.

Study 20210004 Tarlatamab 10 mg includes Study 20210004 1->10 mg. Study 20210004 SOC Chemotherapy includes Study 20210004 amrubicin, lurbinectedin, topotecan. Integrated Analysis Tarlatamab 10 mg includes Study 20210004 1->10 mg; Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); Study 20160323 cohorts 8, 32 and 35. Integrated Analysis Tarlatamab All Doses includes all participants who receive any dose of tarlatamab monotherapy from Studies 20210004, 20200491, and 20160323.
Data snapshot date: 06DEC2024 for Study 20160323; 16DEC2024 for Study 20200491; 13MAR2025 for Study 20210004.
Data cutoff date: 18OCT2024 for Studies 20160323 and 20200491; 29JAN2025 for Study 20210004.
Source: ISS Table 14-2.1.400

Table 16. Applicant – Baseline Disease Characteristics - Studies 20210004, 20200491, and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
ECOG status at baseline - n (%)				
0	83 (32.9)	78 (32.0)	151 (31.9)	240 (32.9)
1	167 (66.3)	164 (67.2)	317 (67.0)	482 (66.0)
2	2 (0.8)	2 (0.8)	5 (1.1)	8 (1.1)
Weight (kg)				
n	252	244	473	730
Mean	72.62	70.22	73.38	74.25
SD	16.27	15.21	16.95	17.42
Median	71.50	68.00	72.00	72.30
Q1, Q3	61.35, 82.00	60.00, 80.00	61.00, 83.30	62.00, 83.55
Min, Max	39.0, 156.5	40.2, 127.0	34.9, 156.5	34.9, 156.5
Smoking history - n (%)				
Never	23 (9.1)	29 (11.9)	42 (8.9)	59 (8.1)
Current	54 (21.4)	49 (20.1)	95 (20.1)	136 (18.6)
Former	175 (69.4)	166 (68.0)	335 (70.8)	533 (73.0)
Missing	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.3)
Number of prior lines of therapy - n (%)				
1	247 (98.0)	237 (97.1)	268 (56.7)	315 (43.2)
2	5 (2.0)	6 (2.5)	138 (29.2)	259 (35.5)
3	0 (0.0)	1 (0.4)	41 (8.7)	88 (12.1)
> 3	0 (0.0)	0 (0.0)	26 (5.5)	66 (9.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)

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Table 12. Applicant – Baseline Disease Characteristics - Studies 20210004, 20200491, and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Number of prior lines of therapy				
n	252	244	473	728
Mean	1.0	1.0	1.7	1.9
SD	0.1	0.2	1.0	1.1
Median	1.0	1.0	1.0	2.0
Q1, Q3	1.0, 1.0	1.0, 1.0	1.0, 2.0	1.0, 2.0
Min, Max	1, 2	1, 3	1, 6	1, 8
Time from initial cancer diagnosis to randomization or enrollment (months)				
n	248	237	455	670
Mean	10.53	11.65	14.06	16.15
SD	6.86	8.70	9.44	12.41
Median	8.57	9.07	11.14	12.58
Q1, Q3	6.83, 11.75	6.97, 12.68	7.92, 17.02	8.38, 20.17
Min, Max	0.7, 54.5	2.3, 84.2	0.6, 61.5	0.6, 131.1
Sum of diameters of target lesions at baseline (mm) - based on investigator assessments				
n	252	244	473	729
Mean	86.566	85.825	93.485	94.089
SD	57.004	53.375	58.254	63.290
Median	71.955	79.130	81.500	81.000
Q1, Q3	42.000, 117.745	42.000, 128.500	48.000, 125.000	48.000, 122.250
Min, Max	10.30, 269.50	11.10, 274.00	10.30, 286.00	10.00, 758.00
Prior PD-1 or PD-(L)1 inhibitor therapy - n (%)				
Yes	179 (71.0)	172 (70.5)	354 (74.8)	514 (70.4)
No	73 (29.0)	72 (29.5)	119 (25.2)	216 (29.6)

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Table 12. Applicant – Baseline Disease Characteristics - Studies 20210004, 20200491, and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Prior radiotherapy for current malignancy - n (%)				
Yes	159 (63.1)	153 (62.7)	330 (69.8)	535 (73.3)
No	93 (36.9)	91 (37.3)	143 (30.2)	195 (26.7)
Prior surgery for current malignancy - n (%)				
Yes	26 (10.3)	24 (9.8)	54 (11.4)	79 (10.8)
No	226 (89.7)	220 (90.2)	419 (88.6)	651 (89.2)
Disease stage at initial diagnosis - n (%)				
Stage 0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage I	5 (2.0)	4 (1.6)	5 (1.1)	6 (0.8)
Stage II	2 (0.8)	4 (1.6)	8 (1.7)	9 (1.2)
Stage III	59 (23.4)	55 (22.5)	81 (17.1)	110 (15.1)
Stage IV	185 (73.4)	181 (74.2)	273 (57.7)	320 (43.8)
Unknown/Missing	1 (0.4)	0 (0.0)	106 (22.4)	285 (39.0)
Disease stage at screening - n (%)				
Stage 0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage II	0 (0.0)	2 (0.8)	3 (0.6)	3 (0.4)
Stage III	21 (8.3)	16 (6.6)	27 (5.7)	37 (5.1)
Stage IV	231 (91.7)	226 (92.6)	434 (91.8)	677 (92.7)
Unknown/Missing	0 (0.0)	0 (0.0)	9 (1.9)	13 (1.8)
Metastatic at baseline - n (%)				
Yes	225 (89.3)	226 (92.6)	438 (92.6)	677 (92.7)
No	27 (10.7)	18 (7.4)	35 (7.4)	53 (7.3)

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Table 12. Applicant – Baseline Disease Characteristics - Studies 20210004, 20200491, and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252)	SOC Chemotherapy (N = 244)	Tarlatamab 10 mg (N = 473)	Tarlatamab All Doses (N = 730)
Brain metastases at baseline - n (%)				
Yes	113 (44.8)	108 (44.3)	166 (35.1)	244 (33.4)
No	139 (55.2)	136 (55.7)	307 (64.9)	486 (66.6)
Liver metastases at baseline - n (%)				
Yes	83 (32.9)	90 (36.9)	176 (37.2)	278 (38.1)
No	169 (67.1)	154 (63.1)	297 (62.8)	452 (61.9)
DLL3 positive - n (%)[a]	205 (95.3)	188 (92.2)	367 (95.3)	573 (95.0)
DLL3 cutpoints - n (%)				
< 75% at 2+ and 3+ staining intensity	118 (46.8)	108 (44.3)	211 (44.6)	313 (42.9)
≥ 75% at 2+ and 3+ staining intensity	97 (38.5)	96 (39.3)	174 (36.8)	290 (39.7)
< 25% at 2+ and 3+ staining intensity	52 (20.6)	50 (20.5)	89 (18.8)	138 (18.9)
≥ 25% at 2+ and 3+ staining intensity	163 (64.7)	154 (63.1)	296 (62.6)	465 (63.7)
Missing	37 (14.7)	40 (16.4)	88 (18.6)	127 (17.4)

The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.
N = Number of participants in analysis set; n = Number of participants with observed data; ECOG = Eastern cooperative oncology group; PD-1 = Programmed death protein 1; PD-(L)1 = Programmed death protein 1 ligand; SOC = Standard of care.
Study 20210004 Tarlatamab 10 mg includes Study 20210004 1->10 mg. Study 20210004 SOC Chemotherapy includes Study 20210004 amrubicin, lurbinectedin, topotecan. Integrated Analysis Tarlatamab 10 mg includes Study 20210004 1->10 mg; Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); Study 20160323 cohorts 8, 32 and 35. Integrated Analysis Tarlatamab All Doses includes all participants who receive any dose of tarlatamab monotherapy from Studies 20210004, 20200491, and 20160323.
Prior surgery for current malignancy does not include biopsies.
Disease stage at initial diagnosis is not available for Study 20160323.
Brain metastases at baseline includes "previous" or "current" brain metastases.
DLL3 positive is defined as participants with 0+ staining intensity < 100.
[a] The percentage for DLL3 positive is based on participants with nonmissing DLL3 results as denominator
Data snapshot date: 06DEC2024 for Study 20160323; 16DEC2024 for Study 20200491; 13MAR2025 for Study 20210004.
Data cutoff date: 18OCT2024 for Studies 20160323 and 20200491; 29JAN2025 for Study 20210004.
Source: ISS Table 14-2.2.400

The Applicant's Position:

Baseline demographics in subjects treated with tarlatamab 10 mg were comparable to tarlatamab all doses data with respect to sex (67.7% men), race (65.8% White [61.9% not Hispanic or Latino] or 30.9% Asian), and age (median [range]: 65.0 [20 to 86] years).

Baseline characteristics in subjects treated with tarlatamab 10 mg were generally consistent with those for the overall population. Subjects had a median (range) of 1 (1 to 6) prior lines of therapy, including prior PD-1 or PD-L1 (74.8%). Most subjects had prior radiotherapy (69.8%). Most subjects had metastatic disease (92.6%), including liver metastases in 37.2% and brain metastasis in 35.1%. Most subjects (67.0%) had an ECOG performance score of 1.

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The FDA's Assessment:

Baseline demographic and disease characteristics for the safety population from DeLLphi-304 and the pooled safety population (473 patients who received tarlatamab 10 mg from DeLLphi-300, DeLLphi-301 and DeLLphi-304) were generally consistent with a patient population with ES-SCLC in the U.S., with the exception of a significantly lower proportion of Black/African American patients and a lower proportion of females relative to the U.S. population with SCLC. Despite these limitations, the overall data is considered supportive of the proposed indication in the U.S. population. A postmarketing commitment (PMC) was issued at the time of the initial approval of tarlatamab for an integrated analysis from ongoing, completed, or planned clinical trials and other potential data sources as appropriate enrolling a sufficient representation of U.S. racial and ethnic minority patients that is reflective of the U.S. population of patients with SCLC, to further characterize the efficacy, safety and pharmacokinetics of tarlatamab in these patients, and this PMC remains open. While the distribution of sex in the U.S. population of patients with SCLC is about 50% each, the subgroup of female patients treated with tarlatamab is large enough to allow for assessments of efficacy and safety in this subgroup; therefore, a PMC to collect additional data in female patients is not considered necessary.

Adequacy of the safety database:

Data:

The safety analysis for the proposed indication is based on safety data from both: (1) pivotal Study 20210004 alone showing the safety of tarlatamab vs SOC chemotherapy and (2) pooled safety data from 3 studies of tarlatamab 10 mg Q2W monotherapy in SCLC (Study 20210004 [pivotal study] and Studies 20200491 and 20160323 [supportive]). As of the data cutoff dates for Studies 20210004, 20200491, and 20160323, a total of 730 subjects were treated with tarlatamab monotherapy across all doses (Table 10). This includes 473 subjects treated with tarlatamab 10 mg dose across Studies 20210004, 20200491, and 20160323.

The Applicant's Position:

The safety database is considered adequate to assess the safety of tarlatamab in the intended indication.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the adequacy of the safety database to support review of this sBLA.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The study centers were monitored by contract research organizations for Studies 20210004, 20200491, and 20160323. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to subject medical and laboratory records was permitted to verify entries on the study-specific electronic case report forms (eCRFs).

Investigator staff training was provided by Amgen Development during investigator meetings, initiation, and routine monitoring visits. The sponsor organized investigator and clinical research associate meetings before study start and during the study to provide information on the investigational product, the study rationale and design, responsibilities under International Conference on Harmonization (ICH) GCP, and training on the detailed study requirements.

Central laboratories were used in the studies. Where local laboratories were used, their participation in internal and external quality control, quality assurance, and accreditation schemes was evaluated by the study monitors.

The investigators were responsible for all data entered in the eCRFs and documented their review and approval of the data by signing a form verifying the validity and completeness of the data. The investigator was responsible for appropriate retention of essential study documents.

Case report form data were captured (via data entry by study center personnel in an Amgen database system [Amgen RAVE Electronic Data Capture]). Data quality checks were applied using manual and electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained.

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that had an effect on the safety review.

The FDA's Assessment:

FDA agrees that the information in the application, including safety datasets and individual case narratives, was adequate to support the safety analysis. There were no data quality or integrity issues identified.

Categorization of Adverse Event

Data:

Not applicable, please see Applicant's position.

The Applicant's Position:

Standard methodologies were used to categorize adverse events. The analyses used Medical Dictionary for Regulatory Activities (MedDRA) version 27.1. For Studies 20210004 and 20200491, CRS and ICANS severity was graded using American Society for Transplantation and Cellular Therapy (ASTCT) guidelines (Lee et al, 2019), and other adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For the monotherapy cohorts of Study 20160323, CRS severity was graded according to Lee et al (2014) and converted to reflect ASTCT guidelines (Lee et al, 2019) where possible; ICANS was reported, but not graded. Other adverse events were converted from CTCAE version 4.0 to version 5.0. A description of the methodology used is provided in the Clinical Events Classification Charter (ISS Module 5.3.5.3). The integrated analyses of safety presented in this dossier do not include adverse events related to disease progression for all studies. Events of interest were evaluated based on search strategies using standardized MedDRA queries (SMQs), Amgen Medical Queries (AMQs), and/or MedDRA System Organ Class (Section 1.1.1 of Module 2.7.4, SCS).

The collection of adverse events in the clinical studies was also appropriate. The protocols defined adverse events and serious adverse events, as well as the reporting procedures. Adverse events were collected after enrollment through the safety follow-up visit. All adverse events considered to be related to investigational product and all serious adverse events regardless of relationship were required to be followed until stabilization or reversibility. Treatment-emergent adverse events were defined as any adverse event with an onset date between the date of first dose and up to and including 65 days after the date of last dose of investigational product or the end of study date, whichever was earlier.

The FDA's Assessment:
FDA generally agrees with the Applicant's description of AE categorization. The FDA review was completed using MedDRA preferred terms (PTs) and custom grouped terms (GTs) when performing independent analyses of AEs on the updated 90 day safety update dataset which was coded using MedDRA 28.0.

Routine Clinical Tests

Data:

In studies 20210004, 20200491, and 20160323, all protocol-required laboratory assessments, including routine hematology and serum chemistry panels, were to be conducted in accordance with the laboratory manual and the schedule of assessments in the protocols. Laboratory values

were graded using the current version of NCI CTCAE and converted if necessary. Clinically significant laboratory abnormalities were to be reported as adverse events. Vital signs, physical measurements, and electrocardiograms (ECGs) were also assessed during study visits as outlined in the schedule of assessments. No statistical analyses of electrocardiogram measurements were performed for Study 20210004. Clinically significant abnormal vital signs or findings were to be reported as adverse events.

The Applicant's Position:

The clinical monitoring of subject safety was considered adequate for the expected toxicities associated with tarlatamab treatment. The time points and analyses of clinical tests were defined in the study protocols.

The FDA's Assessment:
FDA agrees with Applicant's position.

8.2.4. Safety Results

Deaths

Data:

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

Fatal adverse events were reported for 20 subjects (7.9%) in the tarlatamab group and 21 subjects (8.6%) in the SOC group. Treatment-related fatal adverse events were reported for 1 subject (0.4%) in the tarlatamab group and 4 subjects (1.6%) in the SOC chemotherapy group. The single fatal treatment-related adverse event in the tarlatamab group was ICANS (1 subject, 0.4%). Upon Amgen medical review, it was determined that the subject's clinical deterioration and death were likely attributable to severe pneumonia in the context of metastatic SCLC with bronchial obstruction. Due to the presence of significant confounding factors, including 2 episodes of grade 3 pneumonia, it was concluded that pneumonia, rather than CRS or ICANS, was the likely cause of fever, hypotension, subsequent encephalopathy, and death. Subject-level details of the fatal event of ICANS are provided in Section 2.1.3 of SCS and Section 12.2.4 of Study 20210004.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323:

Fatal adverse events were reported for 30 subjects (6.3%) treated with tarlatamab 10 mg. The most frequently reported fatal adverse event by preferred term (occurring in > 1 subject) was pneumonia (6 subjects, 1.3%) (Table 13). Treatment-related fatal adverse events were reported

for 2 subjects (0.4%) treated with tarlatamab monotherapy at 10 mg, one of whom experienced a fatal event of respiratory failure and the other a fatal event of ICANS. Upon Amgen medical review of the fatal event of respiratory failure, the final cause of death was assessed as respiratory failure, considered multifactorial, due to both pneumonitis and severe underlying COPD. Subject-level details of the fatal events of respiratory failure and ICANS are provided in Section 2.1.3 of SCS and Section 12.2.4 of Study 20210004.

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Table 17. Applicant - Fatal Adverse Events by Preferred Term – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Number of participants reporting treatment-emergent fatal adverse events	20 (7.9)	21 (8.6)	30 (6.3)	41 (5.6)
Pneumonia	4 (1.6)	6 (2.5)	6 (1.3)	7 (1.0)
Cardio-respiratory arrest	3 (1.2)	1 (0.4)	3 (0.6)	5 (0.7)
Respiratory failure	1 (0.4)	2 (0.8)	3 (0.6)	4 (0.5)
Aspiration	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.3)
Cardiac arrest	1 (0.4)	3 (1.2)	1 (0.2)	2 (0.3)
Euthanasia	1 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Sepsis	2 (0.8)	0 (0.0)	2 (0.4)	2 (0.3)
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiopulmonary failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

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Footnotes are defined on the last page.

Table 13. Applicant - Fatal Adverse Events by Preferred Term – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323
(Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Chronic obstructive pulmonary disease	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Circulatory collapse	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Coronavirus infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Death	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Dyspnoea	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Gastric haemorrhage	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Haemoptysis	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Hepatic failure	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Immune effector cell-associated neurotoxicity syndrome	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)
Myocardial infarction	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Pulmonary oedema	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.1)

Footnotes are defined on the last page.

Table 13. Applicant - Fatal Adverse Events by Preferred Term – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Respiratory acidosis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Seizure	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Arteriovenous fistula site haemorrhage	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Febrile neutropenia	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
General physical health deterioration	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Hepatotoxicity	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Pneumonia aspiration	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Pneumonitis	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory tract infection	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Sudden death	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Tumour lysis syndrome	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.
N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.
Study 20210004 Tarlatamab 10 mg includes Study 20210004 1->10 mg. Study 20210004 SOC Chemotherapy includes Study 20210004 amrubicin, lurbinectedin, topotecan. Integrated Analysis Tarlatamab 10 mg includes Study 20210004 1->10 mg; Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); Study 20160323 cohorts 8, 32 and 35. Integrated Analysis Tarlatamab All Doses includes all participants who receive any dose of tarlatamab monotherapy from Studies 20210004, 20200491, and 20160323.

Coded using MedDRA version 27.1.
Events of small cell lung cancer/disease progression are excluded.
Data snapshot date: 06DEC2024 for Study 20160323; 16DEC2024 for Study 20200491; 13MAR2025 for Study 20210004.
Data cutoff date: 18OCT2024 for Studies 20160323 and 20200491; 29JAN2025 for Study 20210004.
Source: *Table 11 of Module 2.7.4, SCS and ISS Table 14-6.8.406*

The Applicant's Position:

Review of fatal adverse events across the tarlatamab clinical development program as of the data cutoff dates did not identify any meaningful trends suggesting a causal association between tarlatamab use and fatalities. Fatal adverse events occurred at a similar rate in the tarlatamab and SOC chemotherapy groups in Study 20210004 (7.9% tarlatamab, 8.6% SOC). Overall, the incidence of fatal adverse events was consistent across the integrated analysis and the tarlatamab arm of Study 20210004, with no trend identified.

The FDA's Assessment:

FDA performed an independent analysis of deaths that occurred in the DeLLphi-304 trial and generally agrees with the Applicant's summary described above.

FDA reviewed the case narratives provided by the Applicant for AEs leading to death. Based on review of the narratives, it was determined that for 19 patients who experienced AEs leading to death, tarlatamab could not be excluded as possibly contributing to death as described below.

Based on FDA's assessment, fatal adverse reactions occurred in 8% of patients receiving tarlatamab; this included one fatal adverse reaction of ICANS. Fatal adverse reactions occurring in more than one patient included pneumonia (1.6%), cardio-respiratory arrest (1.6%), and sepsis (0.8%).

Summaries for all patients who experienced fatal AEs along with FDA assessment for each case are presented below.

- Patient (b) (6) was a 72-year-old female with a medical history of right breast cancer, chronic obstructive pulmonary disease (COPD) requiring Continuous Positive Airway Pressure (CPAP), obstructive sleep apnea, dyslipidemia, and osteoporosis. One day after starting tarlatamab, the patient presented with grade 3 pneumonia. Three days later, pneumonia was reported as resolved and the patient was discharged on oral cefixime and fluconazole. After 3 days, the patient was hospitalized again due to grade 3 pneumonia. Symptoms included grade 3 fever, cough with sputum, vomiting (bilious), and grade 3 asthenia. Chest X-ray confirmed persistent consolidation, and antibiotics were escalated to piperacillin/tazobactam.

  Two days after hospitalization, the patient received the second dose of tarlatamab for cycle 1 day 8, and on the following day, the patient the patient experienced clinical deterioration, grade 2 CRS, somnolence, and episodes of disorientation. Chest imaging continued to show left lung consolidation. Five days later, the patient was diagnosed with Grade 1 ICANS. The electroencephalogram (EEG) demonstrated focal epileptiform activity and diffuse slowing. Neurology consultation stated that it was not entirely clear that the episode was related to a seizure and encephalopathy was suspected. Two days

later, CRS worsened to grade 3 with symptoms including fever, hypotension, hypoxemia, and decreased level of consciousness. Tocilizumab was administered and the patient was also treated with including piperacillin/tazobactam, fluconazole, midazolam. The patient showed slight improvement in neurological symptoms post-tocilizumab but remained somnolent. Two days later, the patient was unresponsive, with rhythmic motor movements (sucking, head rotation). An EEG showed non-convulsive seizures and levetiracetam was started. Due to the patient's poor prognosis and non-candidacy for intensive care unit admission, palliative sedation was initiated in agreement with the family. Despite treatment, the patient's neurological status further declined. The patient died the following day with the final cause of death was reported as ICANS, secondary to tarlatamab. No autopsy was performed. The investigator assessed the event of pneumonia as not related to tarlatamab. The investigator assessed the event of ICANS and CRS as possibly related to tarlatamab.

FDA Assessment: The patient's signs and symptoms were consistent with CRS and ICANs which are both toxicities associated with tarlatamab therapy. In addition, the investigator considered the events possibly related to tarlatamab. Given the details of this case, the FDA cannot exclude tarlatamab as possibly contributing to the patient's death.

- Patient (b) (6) was a 56-year-old male with a medical history of congenital fusion of C5-C6 vertebrae, claustrophobia, keratoconus, cataract, cough, benign prostatic hyperplasia, chest pain and axillary pain. Two hundred days after starting tarlatamab and and 31 days after the last dose of tarlatamab, the patient developed grade 3 pneumonia and was hospitalized in the intensive care unit. The investigator reported that the site contacted the patient by phone due to absence from a scheduled appointment and was informed by the patient's wife about the hospitalization due to pneumonia. No treatment information was received. Nine days later, it was reported that the patient died. According to the death certificate, the cause of death was reported as septic shock, sepsis, pneumonia and lung neoplasia. No autopsy was reported. The investigator reported that there were no further details of treatment provided for the event available and about the status of underlying disease (SCLC). The investigator assessed pneumonia as not related to tarlatamab.

  FDA Assessment: The lack of details regarding the diagnostic workup for diagnosing pneumonia, the treatments received and the course of the event, FDA cannot exclude tarlatamab as contributing to the patient's death.

- Patient (b) (6) was a 68-year-old male with a medical history of nausea, emesis, sinus tachycardia, hypertension, increased thyroid stimulating hormone, positive urine occult blood, hyperglycemia and increased GGT. Two days after the first dose of tarlatamab, the patient reported abdominal distention and was treated with glycerin

enema to assist with defecation. About 2.5 hours later, the patient's family called the nurse who immediately checked on the patient but he was found unresponsive. The patient developed grade 4 depressed level of consciousness, characterized as "failed to respond to breath, palpated aortic pulsation was weak" with bradycardia (heart rate 47/min) and hypoxemia (oxygen saturation 69%). External chest compressions were started but the patient continued to deteriorate. The family declined further resuscitation and requested for the patient to be discharged. The patient was unconscious upon discharge and his living state was unknown when he left the hospital accompanied by his family. The next day, it was reported that the patient went into cardio-respiratory arrest. According to the death certificate, the cause of death was cardio-respiratory arrest. No autopsy was performed.
The investigator assessed the event of depressed level of consciousness as possibly related to tarlatamab, and the events of cardio-respiratory arrest as not related to tarlatamab.

FDA Assessment: The patient had symptoms consistent with potential neurologic toxicity which is a known toxicity of tarlatamab. Given the lack of further diagnostic workup and treatments, FDA cannot exclude tarlatamab as contributing to the patient's death.

- Patient (b) (6) was a 53-year-old male with a medical history of chest discomfort, dyspnea, and asthenia. Ninety one days after the first dose of tarlatamab and 7 days after the last dose tarlatamab, the patient requested to be withdrawn from the study and consented only to vital status information collection. Tarlatamab treatment was discontinued. Ongoing adverse events at the time of discharge were grade 1 cough, hematuria, renal calcification and grade 2 anorexia, dysgeusia. Twenty one days later, the patient died at home; the cause of death was unknown, and it was not reported whether an autopsy was performed. No further clinical details were available. The investigator assessed the event of death as not related to tarlatamab.

  FDA Assessment: The patient withdrew consent and given the lack of surrounding details regarding the patient's death, FDA cannot exclude tarlatamab as contributing to the patient's death.

- Patient (b) (6) was a 64-year-old female with a medical history of chronic obstructive pulmonary disease, hypertension, bilateral vocal fold paralysis, "marbled skin on abdomen", abdominal distension and prior cerebral aneurysm. Seventy nine days after the first dose of tarlatamab and 37 days after the last dose tarlatamab, the patient presented to the emergency room with gastric bleeding, was diagnosed with a grade 4 gastric haemorrhage, was hospitalized and underwent an operation on the same day. The following day, the patient experienced a recurrent gastric hemorrhage and died. No additional treatment details were reported. The death certificate was not available, and it

was not known if an autopsy was performed. No action was taken with tarlatamab for the event of gastric haemorrhage. The investigator assessed the events of gastric haemorrhage as not related to tarlatamab.

FDA Assessment: The patient's medical history does not suggest any risk factors for gastric hemorrhage and it is unclear from the narrative what caused this event. Given the lack of additional details, FDA cannot definitively exclude tarlatamab from contributing to the patient's death.

- Patient (b) (6) was a 73-year-old male with a medical history of hypertension, heart failure, diabetes, hypothyroidism, anemia and prior right carotid occlusion and myocardial infarction. One hundred fourteen days after the first dose of tarlatamab and 30 days after the last dose tarlatamab, the patient developed cardio-respiratory arrest and died the same day. Tarlatamab treatment was discontinued due to disease progression, 30 days before the patient died. No autopsy or additional treatment details were reported. No action was taken with tarlatamab for the event of cardio-respiratory arrest. The investigator assessed the event of cardio-respiratory arrest as not related to tarlatamab.

  FDA Assessment: While the patient's medical history indicate prior diagnoses of cardiac disease, and the presence of disease progression, given the lack of additional information regarding the event of cardio-respiratory arrest, the FDA cannot exclude tarlatamab from contributing to the patient's death.

- Patient (b) (6) was a 69-year-old female with a medical history of insomnia. Fifty days after the first dose of tarlatamab and 29 days after the last dose tarlatamab, the patient had a cardio-respiratory arrest due to underlying disease and died the same day. Tarlatamab treatment was discontinued due to progression of the patient's disease 8 days before patient death. No autopsy or additional treatment information was available. No action was taken with tarlatamab for the event of cardio-respiratory arrest. The investigator assessed the event of cardio-respiratory arrest as not related to tarlatamab.

  FDA Assessment: While the patient experienced disease progression, given the lack of additional details surrounding the event of cardio-respiratory arrest, FDA cannot exclude tarlatamab from contributing to the patient's death.

- Patient (b) (6) was a 67-year-old male with a medical history of hypercholesteremia. Tarlatamab treatment was discontinued due to progression of the patient's disease. One hundred twenty nine days after the first dose of tarlatamab and 17 days after the last dose tarlatamab, tarlatamab was discontinued due to interstitial pneumonia. Six days later, the patient developed grade 3 dyspnea and was hospitalized with severe acute respiratory failure requiring high-flow nasal cannula. Despite

supportive therapy, the patient's dyspnea worsened, and six days later the patient went into cardiac arrest and died the same day. No autopsy was performed. No action was taken with tarlatamab for the events of dyspnea and cardiac arrest as treatment had already been discontinued. The investigator assessed the event of dyspnea as possibly related to tarlatamab. The event of cardiac arrest was assessed as not related to tarlatamab.

FDA Assessment: It appears that the dyspnea and subsequent cardiac arrest may have been possibly caused by the interstitial pneumonia that caused the patient to discontinue treatment with tarlatamab. Given this, FDA cannot exclude tarlatamab as contributing to the patient's death.

- Patient (b) (6) was a 72-year-old female with a medical history of hypertension, diabetes mellitus, and exertional dyspnea. On the same day that tarlatamab was administered (8.5 hours the dose), the patient developed grade 3 CRS with symptoms that included fever and hypotension and was treated with intravenous fluids, dexamethasone, and norepinephrine. Later on the same day, the patient also developed confusion. The following day, the patient experienced worsening confusion, aphasia, and aggravated hypotension, requiring tocilizumab and additional vasopressor support. Later that evening, while the patient's aphasia and confusional state resolved, the patient progressed to coma. The following day, the patient developed circulatory collapse and died despite intensive management. The investigator initially considered the events of coma, aphasia, hypotension, and confusional state as possibly related to tarlatamab, with coma suspected to represent immune effector cell-associated neurotoxicity syndrome (ICANS) concurrent with cytokine release syndrome but later concluded that coma and circulatory collapse were more likely due to a cardiovascular event such as stroke. The investigator ruled out ICANS based on lack of confirmatory neurologic testing, atypical progression pattern (confusion/aphasia resolved before coma), and documented hypertensive peaks with tachycardia suggesting vascular rather than inflammatory mechanisms. Given the patient's cardiovascular risk factors (hypertension, diabetes), the investigator concluded death was most consistent with an acute stroke rather than tarlatamab-related toxicity.The final assessment was that circulatory collapse, coma, aphasia, and confusional state were not related to tarlatamab, while hypotension was possibly related to tarlatamab..

  FDA Assessment: It is not clear how the investigator reached the conclusion that these events were due to a cardiovascular event. From the narrative, these events could possibly be consistent with ICANS concurrent with CRS. FDA cannot definitively exclude tarlatamab as contributing to the patient's death.

- Patient (b) (6) was a 65-year-old male with a medical history of diabetes mellitus, hypertension, angina pectoris, and bilateral adrenal hyperplasia. Three hundred thirty eight days after the first dose of tarlatamab and 31 days after the last dose of tarlatamab, the patient developed pneumonia and was confirmed positive for COVID-19 by an antigen test and was hospitalized. Despite treatment including antibiotics, remdesivir, and supportive measures, the patient developed progressive hypoxemia with diffuse bilateral ground-glass opacities on chest X-ray. Six days later, the patient died of pneumonia and COVID-19; both events were reported as fatal. No autopsy was performed. The investigator assessed the events of pneumonia and COVID-19 as not related to tarlatamab.

  FDA Assessment: Given the patient was positive for COVID-19, it appears plausible that the patient died from COVID-19 pneumonia; however, FDA cannot exclude the contribution of tarlatamab to the patient's death.

- Patient (b) (6) was a 80-year-old male with a medical history of hypertension, diabetes mellitus, dyslipidemia, benign prostatic hyperplasia, esophagitis, left internal carotid artery occlusion, knee pain, back pain (spinal stenosis was ruled out), cough, and sputum. On the same day the patient received the first dose of tarlatamab, the patient developed grade 3 pneumonia and was hospitalized 2 weeks later for supportive treatment including percutaneous catheter drainage and antibiotics. Chest X-ray showed right pleural effusion. Laboratory values at this time included high-sensitivity C-Reactive Protein (hs-CRP) 6.48 mg/dl and oxygen saturation 91%. Tarlatamab was temporarily withheld due to the event.

  One week later, during hospitalization, the patient developed chest pain, and the following day was diagnosed with unstable angina. ECG revealed V2-6 T wave inversion and cardiac markers were abnormal: Creatine Kinase–Myocardial Band (CK-MB) 2.26 ng/mL, troponin T 119 ng/L, and PRO-BNP >35,000 pg/mL. Coronary angiography and percutaneous coronary intervention were performed. Six days later, the patient developed grade 3 acute kidney injury with laboratory findings including creatinine 3.84 mg/dl, Blood Urea Nitrogen (BUN) 44 mg/dl, and hs-CRP 11.5 mg/dl. The patient was admitted to the intensive care unit and treated with continuous renal replacement therapy, antibiotics (ceftriaxone, levofloxacin, vancomycin, meropenem, piperacillin/ tazobactam), and supportive measures. The event of unstable angina was reported as resolved. Despite these interventions, the patient's condition worsened, and the patient died due to pneumonia and acute kidney injury. No autopsy was performed. The primary cause of death was reported as pneumonia, with acute kidney injury as contributing factor. The outcome of the event acute kidney injury was ongoing at the time of the death. The investigator reported that pneumonia, acute kidney injury, and unstable angina were not related to tarlatamab.

FDA Assessment: The patient developed pneumonia on the same day of receiving tarlatamab therapy. Despite his advanced age, given the details of this case, FDA cannot exclude contribution of tarlatamab to the patient's death.

- Patient (b) (6) was a 76-year-old male with a medical history of cough, constipation, dyspepsia, anorexia and bilateral cataracts. Three hundred seventeen days after the first dose of tarlatamab and 23 days after the last dose of tarlatamab, the patient developed grade 4 febrile neutropenia, sepsis, and multiple organ dysfunction syndrome. Laboratory tests showed platelets 179 ×10^9/L, absolute neutrophil count 0.01 ×10^9/L, bilirubin 1.9 mg/dL, creatinine 1.05 mg/dL, blood urea nitrogen 21.5 mg/dL, and C-reactive protein 24.47 mg/dL. The following day, the patient was hospitalized and treated with intravenous antibiotics, hydration, and granulocyte colony-stimulating factor (G-CSF, filgrastim). The patient died 6 days later, with grade 5 sepsis. The event of multiple organ dysfunction syndrome and febrile neutropenia was reported as resolved. No autopsy was reported. The investigator reported that all events (febrile neutropenia, sepsis, multiple organ dysfunction syndrome, and neutropenia) were not related to tarlatamab.

  FDA Assessment: Although the onset of the event was almost one year after starting treatment, tarlatamab has been associated with neutropenia as per Section 5 of the label. Given this, FDA cannot exclude tarlatamab as contributing to the patient's death.

- Patient (b) (6) was a 51-year-old male with a medical history of hypertension, dyslipidemia, chronic obstructive pulmonary disease, anemia, superior vena cava syndrome, hemoptysis, and liver enzymes increased. Twenty seven days after the first dose of tarlatamab and 11 days after the last dose of tarlatamab, the patient presented to the emergency department with dyspnea and chest pain. CT angiography showed no pulmonary embolism but revealed a large right mediastinal mass crossing the midline with vascular infiltration, total atelectasis of the right lung, increased right pleural effusion, and multiple bone and liver lesions, consistent with disease progression. Laboratory tests included AST 356 IU/L, ALT 308 IU/L, and platelets 56,000/µL, all of them were assessed as related to disease progression. The following day, the patient was admitted with worsening symptoms. In the afternoon, the patient developed massive hemoptysis attributed to tumor infiltration, leading to cardiorespiratory arrest and death. The cause of death was reported as hemoptysis secondary to disease progression. No autopsy was performed. No action was taken with tarlatamab. The investigator reported that the event of hemoptysis was not related to tarlatamab however it was secondary to the progression of the tumor.

FDA Assessment: Given the progression noted on imaging and worsening labs, it is likely that the patient experienced disease progression. However, given the details of this case, FDA cannot exclude the contribution of tarlatamab to the patient's death.

- Patient (b) (6) was a 67-year-old male with a medical history of COPD. One hundred fourteen days after the first dose of tarlatamab and 13 days after the last dose of tarlatamab, the patient developed grade 2 pleural effusion and tarlatamab was interrupted for this event. He was hospitalized the same day for grade 4 dyspnea. The chest X-ray revealed right pleural effusion. Laboratory findings included pro-BNP 400, CRP 70 mg/L. A pleural puncture drained 300 cc but symptoms did not improve. Despite furosemide and CPAP therapy, the patient remained in respiratory distress with hypercapnic acidosis [pH 7.32, PCO_2 6, arterial oxygen partial pressure (PaO_2) 11 kPa]. The patient declined transfer to intermediate care and accepted the prognosis. The following day, the patient developed grade 4 pulmonary oedema with worsening dyspnea. Labs showed BNP 900 ng/L, CRP 75 mg/L, troponin 31 ng/L, and leukocytes 13 g/L. Despite high-flow oxygen, IV furosemide, morphine, acetaminophen, ketorolac, and initiation of palliative sedation with midazolam, symptoms persisted. Two days later, the patient further deteriorated, the event pulmonary edema progressed, and the patient died. The cause of death was reported as pulmonary edema with hypercapnic acidosis attributed to disease progression. Tumor assessment was performed on (b) (6) but was marked not evaluable. No autopsy was performed. No action was taken with tarlatamab for the event of pulmonary edema. The investigator reported pleural effusion and pulmonary edema as not related to tarlatamab and was reported to be due to disease progression.

  FDA Assessment: Given the available information, it is unclear if this patient's pulmonary effusion was due to disease progression, as there is no report of positive cytology and the narrative also describes pulmonary edema. FDA cannot exclude the contribution of tarlatamab to the patient's death.

- Patient (b) (6) was a 57-year-old male with a medical history of stomach pain, depression, and atrial fibrillation. On the same day as the first dose of tarlatamab, the patient developed worsening dyspnea, with partial oxygen pressure reduced to 83. ECG showed atrial fibrillation with rapid ventricular response (heart rate 123/min). The patient was admitted for observation, and subsequently intubated and cardioverted following hemodynamic deterioration. The patient was transferred to an external intensive care unit due to the unavailability of beds at the site. Treatments administered included dexamethasone, amiodarone, midazolam, fluids, and isotopes. Despite interventions, the patient's hemodynamic status did not improve. Two days later, the patient had cardiopulmonary arrest and died. The cause of death was reported as dyspnea. The investigator reported that dyspnea was not related to tarlatamab but rather related to the

patient's clinical status. An autopsy was not performed, and no final diagnostic clarification was made.

FDA Assessment: While the investigator's assessment of clinical status is plausible. Shortness of breath and low oxygen pressure may also be signs of CRS, a known toxicity of tarlatamab. Given this, FDA cannot definitively preclude tarlatamab as contributing to the patient's death.

- Patient (b) (6) was a 74-year-old male with a medical history of COPD, hypothyroidism, anemia, body pain, and somatomedin C increase. Three weeks after the first dose of tarlatamab, the patient developed grade 3 anorexia that persisted. Two hundred eighty three days after the first dose of tarlatamab and 21 days after the last dose of tarlatamab, the patient presented to the emergency department with diarrhea, anorexia, and oral intake disorder. He was observed in the emergency unit until the following day and was then admitted to the ward. Laboratory tests showed white blood cell (WBC) 10.8 $\times 10^3/\mu L$, hemoglobin (Hb) 11.6 g/dL, CRP 78.74 mg/L, and albumin 27.6 g/L. Troponin T was elevated (41.75 → 48.08 ng/L). Imaging revealed thoracic infectious pathology and abdominal free fluid.

  Three days later, the patient's condition worsened, with CRP rising to 114.71 mg/L, procalcitonin 0.228 µg/L, and ECOG decline. The following day, labs showed WBC 11.1 $\times 10^3/\mu L$, red blood cell (RBC) 2.88 $\times 10^6/\mu L$, Hb 9.3 g/dL, and CRP 109.89 mg/L. Two days later, the patient developed dyspnea with hypotension (84/64 mmHg). The following day, labs revealed WBC 27.7 (unit not specified), Hb 9.5 g/dL, RBC 3 $\times 10^6/\mu L$, albumin 16.5 g/L, creatinine 1.5 mg/dL, urea 74 mg/dL, glucose 273 mg/dL, AST 148 U/L, ALT 118 U/L, potassium 5.4 mmol/L, and phosphorus 8.4 mg/dL. The patient was transferred to the intensive care unit with sepsis. Despite treatment with antibiotics (ceftriaxone, clarithromycin, meropenem, teicoplanin), bronchodilators (ipratropium/salbutamol, budesonide), supportive therapies (albumin, calcium, vitamins, electrolytes, nutritional supplements), steroids, vasopressors (norepinephrine), and anticoagulation (enoxaparin), the patient deteriorated. The patient died due to sepsis, secondary to gastroenteritis, pneumonia, anorexia, and underlying SCLC with brain metastases. The investigator reported that sepsis, gastroenteritis, pneumonia, and decreased appetite were not related to tarlatamab.

  FDA Assessment: From the narrative, it appears plausible that the patient died from an infection, with high white blood counts; tarlatamab cannot be excluded from contributing to the patient's death.

- Patient (b) (6) was a 59-year-old female with a medical history of anxiety disorder, psoriasis, insulin resistance, anemia, and lymphopenia. Twenty two days after

the first dose of tarlatamab and 48 hours after the last dose of tarlatamab, the patient developed a grade 1 pyrexia (38.7°C) and was hospitalized. The pyrexia persisted for 2 days and the patient was discharged. However, one hour after discharge, the patient developed hypoxia with oxygen saturation 50% and was readmitted and transferred to ICU. ECG showed sinus tachycardia; laboratory tests included CK-MB 3.9 ng/mL, D-dimer 7.09 µg/mL, troponin I 8.1 ng/L, procalcitonin 27.15 ng/mL rising to 58.48 ng/mL, and GGT up to 443 U/L. Imaging revealed new left lung opacities, 4 cm pleural effusion, bronchograms, and consolidation zones consistent with pneumonia. Cultures showed no bacterial growth but low Candida species.

The patient required respiratory support, broad-spectrum antibiotics (piperacillin/tazobactam, meropenem, vancomycin, colistin), steroids, anticoagulation, antifungals (fluconazole), and multiple supportive medications (albumin, norepinephrine, midazolam, propofol, nutritional support, diuretics, electrolytes). Despite ICU management, the patient's condition deteriorated and the patient died 12 days after being readmitted. The cause of death was reported as pneumonia. Pyrexia was reported as possibly related to tarlatamab. The investigator assessed pneumonia as not related to tarlatamab.

FDA Assessment: From the narrative, it appears plausible that the patient died from an infection. FDA cannot exclude contribution of tarlatamab to the patient's death.

- Patient (b) (6) was a 79-year-old male with a medical history of COPD, emphysema, hypertension, hyperlipidemia, type 2 diabetes mellitus, dyspepsia, benign prostatic obstruction, insomnia, back pain, glaucoma, cataracts, prostate cancer, constipation, fatigue, and peripheral sensory neuropathy. Twenty two days after the first dose of tarlatamab and 7 days after the last dose of tarlatamab, the patient presented to the emergency department with altered mental status, diarrhea, worsening dyspnea on exertion, and oxygen desaturation. Vitals included 198/92 (units not reported), heart rate 83, and SpO_2 54% on room air (improved to 94% on 3L nasal canula). Sodium was 123 mmol/L (baseline 137 mmol/L [grade 3]). CT angiography was negative for pulmonary embolism but suggested left upper lobe pneumonia. The patient was admitted to the medical ICU the following day, received IV antibiotics (vancomycin, piperacillin/tazobactam), sodium chloride bolus (3%), and supportive care. During hospitalization, the patient continued to experience COPD symptoms and was treated with IV antibiotics and supportive respiratory therapies, including inhalers and steroids. Hyponatremia had resolved 4 days later and the patient was discharged 11 days after hyponatremia had resolved but remained in frail condition. Three days after discharge, died from exacerbation of COPD. The investigator reported that hyponatremia was possibly related to tarlatamab, while COPD exacerbation was not related to tarlatamab. No autopsy was performed.

FDA Assessment: Tarlatamab cannot be excluded from contributing to the patient's death.

- Patient (b) (6) was a 77-year-old male with a medical history of coronary artery disease, congestive heart failure, hypertension, hyperlipidemia, benign prostatic hyperplasia, bilateral lower leg edema, and ALT/AST elevation. Twenty seven days after the first dose of tarlatamab and 8 days after the last dose of tarlatamab, the patient developed worsening shortness of breath and weakness (grade 4 dyspnea). Oxygen saturation was 93% on 3L home oxygen. CT chest showed no pulmonary embolism but extensive mass-like consolidation of the left lower lobe with airway obstruction, likely a combination of malignancy and superimposed pneumonia. Chest X-ray confirmed dense consolidation with pleural effusion. The patient was hospitalized, initiated on bilevel positive airway pressure, and treated with vancomycin, piperacillin/tazobactam, and supportive care. Despite treatment, the patient's respiratory function deteriorated. The patient's hospital course was complicated by acute kidney injury (elevated creatinine, anuria, hyperkalemia), requiring supportive and comfort care including diuretics, opioids (morphine, hydromorphone), and palliative measures. The patient died 5 days later due to respiratory failure secondary to progressive SCLC with superimposed pneumonia. No autopsy was performed. The investigator reported that dyspnea and respiratory failure were not related to tarlatamab.

  FDA Assessment: From the narrative, it appears plausible that the patient died from an infection. Given the details of this case, tarlatamab cannot be excluded from contributing to the patient's death.

Serious Adverse Events

Data:

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

Serious adverse events were reported for 129 subjects (51.2%) in the tarlatamab group and 125 subjects (51.2%) in the SOC chemotherapy group in Study 20210004. The most common serious adverse events (≥ 5 subjects in either group) for tarlatamab were: CRS (43 subjects, 17.1%), pyrexia (14 subjects, 5.6%), pneumonia (10 subjects, 4.0%), ICANS (9 subjects, 3.6%), dyspnea (6 subjects, 2.4%), and febrile neutropenia, hyponatremia, and sepsis (5 subjects, 2.0% each). In the SOC chemotherapy group, these included: febrile neutropenia (24 subjects, 9.8%), pneumonia (21 subjects, 8.6%), thrombocytopenia (11 subjects, 4.5%), anemia (10 subjects, 4.1%), neutropenia and platelet count decreased (6 subjects, 2.5% each), and pancytopenia (5

subjects, 2.0%). Treatment-related serious adverse events were reported for 70 subjects (27.8%) in the tarlatamab group and 75 subjects (30.7%) in the SOC group.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323:

The subject incidence of serious adverse events that occurred in ≥ 1% of subjects in the Safety Analysis Set is provided in Table 14.

Serious adverse events were reported for 256 subjects (54.1%) treated with tarlatamab 10 mg. The most frequently reported serious adverse events (≥ 3% of subjects) by preferred term were CRS (93 subjects [19.7%]), pyrexia (22 subjects [4.7%]), and pneumonia (18 subjects [3.8%]).

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Table 18. Applicant - Serious Adverse Events by Preferred Term Occurring in at Least 1% of Subjects Across Tarlatamab All Doses – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Number of participants reporting treatment-emergent serious adverse events	129 (51.2)	125 (51.2)	256 (54.1)	416 (57.0)
Cytokine release syndrome	43 (17.1)	1 (0.4)	93 (19.7)	170 (23.3)
Pyrexia	14 (5.6)	0 (0.0)	22 (4.7)	34 (4.7)
Pneumonia	10 (4.0)	21 (8.6)	18 (3.8)	32 (4.4)
Hyponatraemia	5 (2.0)	4 (1.6)	12 (2.5)	22 (3.0)
Immune effector cell-associated neurotoxicity syndrome	9 (3.6)	0 (0.0)	13 (2.7)	22 (3.0)
Dyspnoea	6 (2.4)	2 (0.8)	7 (1.5)	13 (1.8)
Fatigue	4 (1.6)	1 (0.4)	7 (1.5)	12 (1.6)
Confusional state	1 (0.4)	0 (0.0)	1 (0.2)	9 (1.2)
Encephalopathy	0 (0.0)	0 (0.0)	1 (0.2)	9 (1.2)

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Table 14. Applicant - Serious Adverse Events by Preferred Term Occurring in at Least 1% of Subjects Across Tarlatamab All Doses – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Febrile neutropenia	5 (2.0)	24 (9.8)	7 (1.5)	9 (1.2)
COVID-19	2 (0.8)	0 (0.0)	3 (0.6)	8 (1.1)
Respiratory failure	2 (0.8)	3 (1.2)	5 (1.1)	7 (1.0)
Superior vena cava syndrome	0 (0.0)	4 (1.6)	5 (1.1)	7 (1.0)

The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.
N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.
Study 20210004 Tarlatamab 10 mg includes Study 20210004 1->10 mg. Study 20210004 SOC Chemotherapy includes Study 20210004 amrubicin, lurbinectedin, topotecan. Integrated Analysis Tarlatamab 10 mg includes Study 20210004 1->10 mg; Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); Study 20160323 cohorts 8, 32 and 35. Integrated Analysis Tarlatamab All Doses includes all participants who receive any dose of tarlatamab monotherapy from Studies 20210004, 20200491, and 20160323.
Coded using MedDRA version 27.1.
Events of small cell lung cancer/disease progression are excluded.
Data snapshot date: 06DEC2024 for Study 20160323; 16DEC2024 for Study 20200491; 13MAR2025 for Study 20210004.
Data cutoff date: 18OCT2024 for Studies 20160323 and 20200491; 29JAN2025 for Study 20210004.
Source: ISS Table 14-6.8.402

The Applicant's Position:

Serious adverse events occurred at the same rate in the tarlatamab and SOC chemotherapy groups in Study 20210004 (51.2% both groups). Overall, no significant differences were observed in incidence of serious adverse events between the integrated analysis and tarlatamab arm in Study 20210004. The serious adverse events were consistent with the known safety profile of tarlatamab.

The FDA's Assessment:

FDA performed an independent analysis of the incidence of SAEs from the DeLLphi-304 trial at the most recent data cutoff provided with the 90-day safety update. Refer to the table below for FDA's analysis of SAEs for DeLLphi-304. Treatment-emergent SAEs occurred in 131 patients (52%) who received tarlatamab and in 126 patients (52%) who received SOC. The most frequently reported SAEs (occurring in >3% of patients) for tarlatamab were CRS (17%), pyrexia (6%), pneumonia (5%) and ICANS (3.6%). An independent analysis of SAEs in the pooled dataset was not performed as this was not used to inform labeling.

Table 19. FDA – Treatment-emergent SAEs Reported in >1% of Patients from DeLLphi-304 (FDA Analysis)

	Tarlatamab (N = 252)	Standard of Care (N = 244)
	n (%)	n (%)
Patients with Serious Treatment Emergent AEs	131 (52)	126 (52)
Cytokine release syndrome	43 (17)	1 (0.4)
Pyrexia	14 (6)	0
Pneumonia (GT)[a]	13 (5)	24 (10)
Immune effector cell-associated neurotoxicity syndrome	9 (3.6)	0
Acute kidney injury	6 (2.3)	0
Dyspnea	6 (2.3)	2 (0.8)
Sepsis	6 (2.3)	2 (0.8)
Fatigue (GT)[b]	5 (2)	2 (0.8)

	Tarlatamab (N = 252)	Standard of Care (N = 244)
	n (%)	n (%)
Febrile neutropenia	5 (2)	24 (10)
Hyponatremia	5 (2)	4 (1.6)
Cardiac arrest (GT)[c]	4 (1.6)	4 (1.6)
Chronic obstructive pulmonary disease	4 (1.6)	0
Arrhythmia (GT)[d]	3 (1.2)	0
Constipation	3 (1.2)	0
Decreased appetite	3 (1.2)	0
General physical health deterioration	3 (1.2)	0.4
Pleural effusion	3 (1.2)	1 (0.8)
Urinary tract infection (GT)[e]	3 (1.2)	2 (0.8)
Neutropenia (GT)[f]	2 (0.8)	9 (3.7)
Musculoskeletal pain (GT)[g]	1 (0.4)	5 (2)
Thrombocytopenia (GT)[h]	1 (0.4)	17 (7)
Anemia	1 (0.4)	10 (4.1)
Superior vena cava syndrome	0	4 (1.6)
Bacterial infection	0	3 (1.2)
Respiratory failure	2 (0.8)	3 (1.2)
Seizure	0	3 (1.2)

[a] Pneumonia (GT) includes PT terms Pneumonia, Pneumonia bacterial
[b] Fatigue (GT) includes PT terms Asthenia, Fatigue
[c] Cardiac arrest (GT) includes PT terms Cardiac arrest, Cardio-respiratory arrest
[d] Arrhythmia (GT) includes PT terms Sinus bradycardia, Sinus node dysfunction, Sinus tachycardia
[e] Urinary tract infection (GT) includes PT terms Cystitis, Urinary tract infection
[f] Neutropenia (GT) includes PT terms Neutropenia, Neutrophil count decreased
[g] Musculoskeletal pain (GT) includes PT terms Arthralgia, Back pain, Bone pain
[h] Thrombocytopenia (GT) includes PT terms Platelet count decreased, Thrombocytopenia

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

Thirteen subjects (5.2%) in the tarlatamab group and 30 subjects (12.3%) in the SOC chemotherapy group had an adverse event that led to discontinuation of investigational product. In the tarlatamab group, the most common adverse events that led to discontinuation of investigational product (reported for ≥ 3 subjects) was pneumonia (3 subjects, 1.2%). In the SOC chemotherapy group, the most common adverse events that led to discontinuation of investigational product (reported for ≥ 3 subjects) were anemia and cardiac arrest (3 subjects, 1.2% each). Seven subjects (2.8%) in the tarlatamab group and 15 subjects (6.1%) in the SOC group had treatment-related adverse events that led to discontinuation of investigational product.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323:

The subject incidence of adverse events leading to discontinuation of tarlatamab that occurred in ≥ 2 subjects in the Safety Analysis Set is provided in Table 15. Adverse events leading to discontinuation of tarlatamab were reported for 29 subjects (6.1%) treated with tarlatamab 10 mg; the most frequently reported (in ≥ 3 subjects) were CRS and pneumonia (3 subjects, 0.6% each).

Table 20. Applicant - Adverse Events Leading to Discontinuation of Tarlatamab by Preferred Term (Occurring in at Least 2 Subjects Across Tarlatamab all Doses) –Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Number of participants reporting treatment-emergent adverse events leading to discontinuation of tarlatamab	13 (5.2)	0 (0.0)	29 (6.1)	49 (6.7)
Cytokine release syndrome	1 (0.4)	0 (0.0)	3 (0.6)	5 (0.7)
Pneumonia	3 (1.2)	0 (0.0)	3 (0.6)	5 (0.7)
Confusional state	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)
Pneumonitis	1 (0.4)	0 (0.0)	1 (0.2)	3 (0.4)
Acute kidney injury	1 (0.4)	0 (0.0)	2 (0.4)	2 (0.3)
Asthenia	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.3)
COVID-19 pneumonia	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.3)
Dysphagia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Encephalopathy	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)

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Table 15. Applicant - Adverse Events Leading to Discontinuation of Tarlatamab by Preferred Term (Occurring in at Least 2 Subjects Across Tarlatamab all Doses) –Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
Preferred Term	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
Immune effector cell-associated neurotoxicity syndrome	1 (0.4)	0 (0.0)	1 (0.2)	2 (0.3)
Neutrophil count decreased	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Tumour lysis syndrome	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)

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The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.
N = Number of participants in analysis set; n = Number of participants with observed data; SOC = Standard of care.
Study 20210004 Tarlatamab 10 mg includes Study 20210004 1->10 mg. Study 20210004 SOC Chemotherapy includes Study 20210004 amrubicin, lurbinectedin, topotecan. Integrated Analysis Tarlatamab 10 mg includes Study 20210004 1->10 mg; Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); Study 20160323 cohorts 8, 32 and 35. Integrated Analysis Tarlatamab All Doses includes all participants who receive any dose of tarlatamab monotherapy from Studies 20210004, 20200491, and 20160323.
Coded using MedDRA version 27.1.
Events of small cell lung cancer/disease progression are excluded.
Data snapshot date: 06DEC2024 for Study 20160323; 16DEC2024 for Study 20200491; 13MAR2025 for Study 20210004.
Data cutoff date: 18OCT2024 for Studies 20160323 and 20200491; 29JAN2025 for Study 20210004.
Source: ISS Table 14-6.8.410

The Applicant's Position:

In Study 20210004, the incidences of subjects reporting discontinuation of investigational product were low in the tarlatamab (13 subjects, 5.2%) when compared with the SOC chemotherapy (30 subjects, 12.3%). The incidence of adverse events leading to discontinuation of tarlatamab across the studies was low (49 of 730 subjects [6.7%] treated with any dose of tarlatamab in the integrated analysis) with < 1% incidence for any single adverse event leading to treatment discontinuation.

The FDA's Assessment:

In the FDA's analysis of the DeLLphi-304 trial at the most recent data cutoff, TEAEs leading to discontinuation of tarlatamab occurred in 14 patients (6%). The only adverse reaction leading to treatment discontinuation of tarlatamab in >1% of patients was pneumonia (1.2%). Refer to the table below for FDA's analysis of TEAEs leading to discontinuation in DeLLphi-304. An independent analysis of TEAEs leading to discontinuation in the pooled dataset was not performed as this was not used to inform labeling.

Table 21. FDA – Treatment-emergent AEs Leading to Discontinuation Reported in >1% of Patients from DeLLphi-304 (FDA Analysis)

	Tarlatamab (N = 252)	Standard of Care (N = 244)
	n (%)	n (%)
Patients with Treatment Emergent AEs Leading to Discontinuation	14 (6)	31 (13)
Pneumonia	3 (1.2)	2 (0.8)
Cardiac arrest (GT)[a]	0	4 (1.6)
Anemia	0	3 (1.2)

[a] Cardiac arrest (GT) includes PT terms Cardiac arrest, Cardio-respiratory arrest

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

Data:

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

The protocol for Study 20210004 does not allow dose reduction for tarlatamab and only provides guidance for dose interruption. Adverse events that led to dose interruption and/or reduction of

investigational product were reported for 94 subjects (37.3%) in the tarlatamab group and 159 subjects (65.2%) in the SOC chemotherapy group. In the tarlatamab group, the most frequently reported adverse events that led to dose interruption of investigational product (≥ 2% of subjects) were fatigue (9 subjects, 3.6%), neutropenia and pneumonia (8 subjects, 3.2% each), decreased appetite (7 subjects, 2.8%), and COVID-19 and neutrophil count decreased (5 subjects, 2.0% each) in the tarlatamab group. In the SOC chemotherapy group, these included: anemia (41 subjects, 16.8%), neutropenia (37 subjects, 15.2%), thrombocytopenia (22 subjects, 9.0%), febrile neutropenia (20 subjects, 8.2%), leukopenia and fatigue (19 subjects, 7.8% each), neutrophil count decreased (17 subjects, 7.0%), pneumonia and platelet count decreased (14 subjects each, 5.7%), white blood cell count decreased (12 subjects, 4.9%), asthenia (11 subjects, 4.5%), and pyrexia and influenza like illness (5 subjects each, 2.0%). Forty-eight subjects (19.0%) in the tarlatamab group and 134 subjects (54.9%) in the SOC group had treatment-related adverse events that led to dose interruption and/or reduction of investigational product.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323:

Adverse events leading to dose reduction and/or interruption of tarlatamab were reported for 165 subjects (34.9%) treated with tarlatamab 10 mg. The most frequently reported (≥ 2% of subjects) adverse events leading to dose reduction and/or interruption of tarlatamab were fatigue (16 subjects, 3.4%); COVID-19 and pneumonia (11 subjects, 2.3% each); and CRS, neutropenia, and decreased appetite (10 subjects, 2.1% each). Treatment-related adverse events leading to dose reduction and/or interruption of tarlatamab were reported for 77 subjects (16.3%) treated with tarlatamab 10 mg; the most frequently reported (≥ 2% of subjects) were fatigue (11 subjects, 2.3%), CRS and neutropenia (10 subjects, 2.1% each).

The Applicant's Position:

In Study 20210004, the incidence of adverse events that led to dose interruptions was lower with tarlatamab (37.3%) than with SOC chemotherapy (65.2%). Overall, the incidence of dose interruptions due to adverse events were comparable between the integrated analysis and the tarlatamab arm of Study 20210004 data.

The FDA's Assessment:

In the FDA's analysis of the DeLLphi-304 trial at the most recent data cutoff, TEAEs leading to interruption of tarlatamab occurred in 95 patients (38%). One patient was classified as "dose reduced" when they received a 1 mg rechallenge dose instead of proceeding to the target dose, and should be included in the dose interruption count, bringing the total to 96 patients (38%).

The most frequently reported AEs leading to treatment Adverse reactions requiring dosage interruption of tarlatamab in ≥2% of patients were neutropenia (5%), fatigue (4.4%), pneumonia

(4%), decreased appetite (2.8%) and COVID-19 (2%). Refer to the Table below for FDA's analysis of TEAEs leading to interruption for DeLLphi-304. In the FDA analysis, FDA separated out treatment interruption from dose reductions for the SOC arm. Overall, 68 (28%) patients had dose reductions in the SOC arm, while 50% had treatment interrupted. No patients had dose reductions in the tarlatamab arm as this was not allowed per protocol. An independent analysis of TEAEs leading to interruption in the pooled dataset was not performed as this was not used to inform labeling.

Table 22. FDA - Treatment-emergent AEs Leading to Treatment Interruption Reported in ≥2% of Patients from DeLLphi-304 (FDA Analysis)

	Tarlatamab (N = 252)	Standard of Care (N = 244)
	n (%)	n (%)
Patients with Treatment Emergent AEs Leading to Treatment Interruption	96 (38)	123 (50)
Neutropenia (GT)[a]	13 (5)	37 (15)
Fatigue (GT)[b]	11 (4.3)	22 (9)
Pneumonia (GT)[c]	10 (4)	15 (6)
Decreased appetite	7 (2.8)	2 (0.8)
COVID-19	5 (2)	1 (0.4)

[a] Neutropenia (GT) includes PT terms Neutropenia, Neutrophil count decreased
[b] Fatigue (GT) includes PT terms Asthenia, Fatigue
[c] Pneumonia (GT) includes PT terms Lower respiratory tract infection, Pneumonia, Pneumonia aspiration, Pneumonia bacterial

Significant Adverse Events

Data:

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

Grade ≥ 3 adverse events were reported for 136 subjects (54.0%) in the tarlatamab group and 195 subjects (79.9%) in the SOC chemotherapy group. Grade ≥ 3 treatment-related adverse events were reported for 67 subjects (26.6%) in the tarlatamab group and 152 subjects (62.3%) in the SOC chemotherapy group. All grade ≥ 3 adverse events occurring in ≥ 5% of subjects in

either treatment group occurred at a lower incidence in the tarlatamab group compared with the SOC chemotherapy group (tarlatamab vs SOC chemotherapy in order of treatment difference): anemia (4.4% vs 28.7%), neutropenia (6.0% vs 23.4%), leukopenia (1.6% vs 13.9%), thrombocytopenia (0.8% vs 11.5%), febrile neutropenia (2.0% vs 11.5%), platelet count decreased (0.4% vs 8.2%), neutrophil count decreased (4.0% vs 11.5%), fatigue (3.6% vs 7.0%), pneumonia (5.6% vs 8.2%), and hyponatremia (4.8% vs 5.3%).

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323:

Grade ≥ 3 adverse events were reported for 281 subjects (59.4%) treated with 10 mg tarlatamab monotherapy. The most frequently reported (≥5% of subjects) grade ≥ 3 adverse events by preferred term were lymphopenia (29 subjects [6.1%]), and hyponatremia (28 subjects [5.9%]).

The Applicant's Position:

In Study 20210004, grade ≥ 3 adverse events occurred at a lower incidence in the tarlatamab group (54.0%) than in the SOC chemotherapy group (79.9%).

The FDA's Assessment:

FDA performed independent analyses on the DeLLphi-304 safety dataset and summarized the proportion of Grade 3 or 4 AEs that occurred. Grade 3 or 4 AEs occurred in 138 patients (55%) in the tarlatamab arm with the most common Grade ≥3 AEs (≥5%) being neutropenia (10%), pneumonia and fatigue (6% each). The FDA independent analysis is provided in the table below.

Table 23. FDA - Treatment-emergent Grade 3 or 4 AEs in ≥5% of Patients from DeLLphi-304 (FDA Analysis)

	Tarlatamab (N = 252)	Standard of Care (N = 244)
	n (%)	n (%)
Patients with Grade 3 or 4 TEAEs	138 (55)	188 (77)
Neutropenia (GT)[a]	25 (10)	82 (34)
Pneumonia (GT)[b]	16 (6)	20 (8)
Fatigue (GT)[c]	14 (6)	24 (10)
Anemia	12 (4.7)	70 (29)
Thrombocytopenia (GT)[d]	3 (1.2)	47 (19)

	Tarlatamab (N = 252)	Standard of Care (N = 244)
	n (%)	n (%)
Leukopenia (GT)[e]	11 (4.3)	46 (19)
Febrile neutropenia	5 (1.9)	29 (12)
Hyponatremia	12 (4.8)	13 (5)

[a] Neutropenia (GT) includes PT terms Neutropenia, Neutrophil count decreased
[b] Pneumonia (GT) includes PT terms Lower respiratory tract infection, Pneumonia, Pneumonia aspiration, Pneumonia bacterial
[c] Fatigue (GT) includes PT terms Asthenia, Fatigue
[d] Thrombocytopenia (GT) includes PT terms Platelet count decreased, Thrombocytopenia
[e] Leukopenia (GT) includes PT terms Leukopenia, White blood cell count decreased

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

A total of 249 subjects (98.8%) in the tarlatamab group and 243 subjects (99.6%) in the SOC chemotherapy group had at least 1 adverse event; 235 subjects (93.3%) in the tarlatamab group and 223 subjects (91.4%) in the SOC chemotherapy group had adverse events that were considered treatment related by the investigator. Grade ≥ 3 adverse events were reported for 136 subjects (54.0%) in the tarlatamab group (treatment related for 67 subjects [26.6%]) and for 195 subjects (79.9%) in the SOC chemotherapy group (treatment related for 152 subjects [62.3%]). Thirteen subjects (5.2%) in the tarlatamab group and 30 subjects (12.3%) in the SOC chemotherapy group had an adverse event that led to the discontinuation of investigational product, of which 7 subjects (2.8%) in the tarlatamab group and 15 subjects (6.1%) in the SOC chemotherapy group had adverse events that were considered treatment related. One hundred twenty-nine subjects (51.2%) in the tarlatamab group and 125 subjects (51.2%) in the SOC chemotherapy group had serious adverse events, for 70 subjects (27.8%) in the tarlatamab group and 75 subjects (30.7%) in the SOC chemotherapy group, the serious adverse events were considered treatment related. Twenty subjects (7.9%) in the tarlatamab group and 21 subjects (8.6%) in the SOC chemotherapy group had a fatal adverse event; for 1 subject (0.4%) in the tarlatamab group and 4 subjects (1.6%) in the SOC group, the fatal events were considered treatment related.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323:

Adverse events were reported for 470 (99.4%) treated with tarlatamab 10 mg, including 446 subjects (94.3%) with at least 1 treatment-related adverse event. Grade ≥3 adverse events were reported for 281 subjects (59.4%). Serious adverse events were reported for 256 subjects (54.1%). Adverse events leading to discontinuation of tarlatamab were reported for 29 subjects (6.1%). Fatal adverse events were reported for 30 subjects (6.3%).

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Table 24. Applicant - Summary of Adverse Events – Studies 20210004, 20200491 and Monotherapy Cohorts of Study 20160323 (Safety Analysis Set)

	Study 20210004		Integrated Analysis (Studies 20210004, 20200491, and 20160323)	
	Tarlatamab 10 mg (N = 252) n (%)	SOC Chemotherapy (N = 244) n (%)	Tarlatamab 10 mg (N = 473) n (%)	Tarlatamab All Doses (N = 730) n (%)
All treatment-emergent adverse events	249 (98.8)	243 (99.6)	470 (99.4)	726 (99.5)
Grade ≥ 2	228 (90.5)	237 (97.1)	434 (91.8)	675 (92.5)
Grade ≥ 3	136 (54.0)	195 (79.9)	281 (59.4)	449 (61.5)
Grade ≥ 4	41 (16.3)	91 (37.3)	86 (18.2)	128 (17.5)
Serious adverse events	129 (51.2)	125 (51.2)	256 (54.1)	416 (57.0)
Leading to dose interruption and/or reduction of tarlatamab	94 (37.3)	0 (0.0)	165 (34.9)	261 (35.8)
Leading to discontinuation of tarlatamab	13 (5.2)	0 (0.0)	29 (6.1)	49 (6.7)
Serious	11 (4.4)	0 (0.0)	21 (4.4)	37 (5.1)
Nonserious	2 (0.8)	0 (0.0)	8 (1.7)	17 (2.3)
Fatal adverse events	20 (7.9)	21 (8.6)	30 (6.3)	41 (5.6)
Treatment-related treatment-emergent adverse events	235 (93.3)	223 (91.4)	446 (94.3)	689 (94.4)
Grade ≥ 2	170 (67.5)	206 (84.4)	337 (71.2)	538 (73.7)
Grade ≥ 3	67 (26.6)	152 (62.3)	141 (29.8)	249 (34.1)
Grade ≥ 4	12 (4.8)	60 (24.6)	26 (5.5)	46 (6.3)
Serious adverse events	70 (27.8)	75 (30.7)	140 (29.6)	259 (35.5)
Leading to dose interruption and/or reduction of tarlatamab	48 (19.0)	0 (0.0)	77 (16.3)	138 (18.9)
Leading to discontinuation of tarlatamab	7 (2.8)	0 (0.0)	15 (3.2)	30 (4.1)
Serious	5 (2.0)	0 (0.0)	10 (2.1)	22 (3.0)
Nonserious	2 (0.8)	0 (0.0)	5 (1.1)	12 (1.6)
Fatal adverse events	1 (0.4)	4 (1.6)	2 (0.4)	3 (0.4)

The safety analysis set is defined as all participants who receive at least 1 dose of investigational product.

N = Number of participants in analysis set; n = Number of participants with observed data; CRS = Cytokine release syndrome; ICANS = Immune effector cell-associated neurotoxicity syndrome; SOC = Standard of care.
Study 20210004 Tarlatamab 10 mg includes Study 20210004 1->10 mg. Study 20210004 SOC Chemotherapy includes Study 20210004 amrubicin, lurbinectedin, topotecan. Integrated Analysis Tarlatamab 10 mg includes Study 20210004 1->10 mg; Study 20200491 1->10 mg (part 1 randomized arm, part 2, and part 3); Study 20160323 cohorts 8, 32 and 35. Integrated Analysis Tarlatamab All Doses includes all participants who receive any dose of tarlatamab monotherapy from Studies 20210004, 20200491, and 20160323.
Studies 20210004 and 20200491: CRS and ICANS events graded using ASTCT 2019; All other events graded using CTCAE v5.0.
Study 20160323: If relevant information was available, CRS events converted from Lee et al. 2014 to ASTCT 2019; Similarly, all other events converted from CTCAE v4.0 to v5.0.
Event with missing relationship is considered to be treatment-related.
Events of small cell lung cancer/disease progression are excluded.
Data snapshot date: 06DEC2024 for Study 20160323; 16DEC2024 for Study 20200491; 13MAR2025 for Study 20210004.
Data cutoff date: 18OCT2024 for Studies 20160323 and 20200491; 29JAN2025 for Study 20210004.
Source: ISS Table 14-6.7.400

Adverse Reactions

Adverse drug reactions were determined to be those events that were reported in ≥ 15% of subjects with SCLC who were treated with tarlatamab 10 mg Q2W from Study 20210004. In addition to these events, a medical review focused on common, grade ≥ 3, and serious adverse events was conducted. Frequently occurring adverse events were assessed, considering expected incidence in patients with underlying diseases to establish an initial threshold. Additional factors, including temporal association, biological plausibility, and medical judgment, were considered to confirm the final adverse drug reactions. The resulting list of adverse drug reactions for tarlatamab are summarized in Table 17.

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Table 25. Applicant - Adverse Reactions Occurring at ≥ 15% in Subjects with SCLC who Received Tarlatamab 10 mg in Study 20210004[a]

	Standard of Care Overall (N = 244) n (%)		Tarlatamab 10 mg (N = 252) n (%)	
System Organ Class Preferred Term	All Grades	Grades 3 to 4	All Grades	Grades 3 to 4
Blood and lymphatic system disorders				
Anaemia	156 (63.9)	70 (28.7)	78 (31.0)	11 (4.4)
Neutropenia[b]	112 (45.9)	82 (33.6)	47 (18.7)	25 (9.9)
Lymphopenia[b]	21 (8.6)	11 (4.5)	36 (14.3)	17 (6.7)
Gastrointestinal disorders				
Constipation	54 (22.1)	0 (0.0)	72 (28.6)	1 (0.4)
Nausea	78 (32.0)	0 (0.0)	61 (24.2)	1 (0.4)
General disorders and administration site conditions				
Fatigue	74 (30.3)	17 (7.0)	72 (28.6)	9 (3.6)
Pyrexia	27 (11.1)	3 (1.2)	69 (27.4)	3 (1.2)
Immune system disorders				
Cytokine release syndrome	3 (1.2)	0 (0.0)	142 (56.3)	3 (1.2)
Metabolism and nutrition disorders				
Decreased appetite	54 (22.1)	4 (1.6)	89 (35.3)	5 (2.0)
Hyponatraemia	24 (9.8)	13 (5.3)	43 (17.1)	12 (4.8)
Nervous system disorders				
Dysgeusia	4 (1.6)	0 (0.0)	61 (24.2)	0 (0.0)
Headache	21 (8.6)	0 (0.0)	38 (15.1)	0 (0.0)
Immune effector cell-associated neurotoxicity syndrome	2 (0.8)	0 (0.0)	15 (6.0)	1 (0.4)
Tremor	3 (1.2)	0 (0.0)	4 (1.6)	0 (0.0)
Ataxia	1 (0.4)	1 (0.4)	1 (0.4)	0 (0.0)
Neurotoxicity	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Seizure	4 (1.6)	1 (0.4)	1 (0.4)	0 (0.0)
Psychiatric disorders				
Confusional state	3 (1.2)	0 (0.0)	1 (0.4)	1 (0.4)
Delirium	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	28 (11.5)	6 (2.5)	18 (7.1)	7 (2.8)

[a] Adverse reactions occurring at a frequency of < 15% and included as adverse reactions were: immune effector cell-associated neurotoxicity syndrome, tremor, ataxia, neurotoxicity, seizure, confusional state, delirium, and dyspnoea

[b]"Lymphopenia" is combined preferred term of "Lymphopenia" and "Lymphocyte count decreased" and "Neutropenia" is combined preferred term of "Neutropenia" and "Neutrophil count decreased."
The combined preferred terms "Lymphopenia" and "Neutropenia" are classified under system organ class of "Blood and lymphatic system disorders."
Adverse events are coded using MedDRA version 27.1; cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome events are graded using ASTCT 2019 criteria and other adverse events are graded using CTCAE version 5.0. Data cutoff date: 29JAN2025
Source: Table 14-6.3.400 of Study 20210004

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The Applicant's Position:

In Study 20210004, tarlatamab demonstrates a more favorable safety profile compared to SOC. The overall incidence of treatment-emergent adverse events was similar between tarlatamab and SOC arms, however, the incidence of grade ≥ 3, grade ≥ 4 adverse events, events leading to dose interruptions and/or reduction or dose discontinuation were lower in tarlatamab compared with SOC chemotherapy. Overall, the frequencies of treatment-emergent adverse events of tarlatamab is consistent between the integrated safety analysis and the tarlatamab arm of Study 20210004. No significant differences were observed in fatal incidence rates across the data sets.

Adverse events that have been determined by the Sponsor to be associated with tarlatamab, based on the totality of the data, are considered to be adverse drug reactions. In Study 20210004, the identified adverse reactions occurring at a frequency of < 15% are immune effector cell-associated neurotoxicity syndrome, tremor, ataxia, neurotoxicity, seizure, confusional state, delirium, and dyspnoea.

The FDA's Assessment:

The analyses performed in this section are based on the 90 day safety update dataset and differ slightly from what the Applicant has presented. However, FDA agrees with the Applicant's position. The most common AEs from FDA's analysis of the DeLLphi-304 and the pooled safety population (DeLLphi-300, DeLLphi-301 and DeLLphi-302) are provided below. AEs which are better captured by assessment of laboratory data (b) (4) ut relevant data are presented in the laboratory abnormalities table in product labeling.

Table 26. FDA - Treatment-emergent AEs Reported in ≥15% of Patients in DeLLphi-304 (FDA Analysis)

Adverse Reaction	IMDELLTRA[a] (N = 252)		Standard of Care (N = 244)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Immune system disorders				
Cytokine release syndrome[b]	56	1.2	1.2	0

Adverse Reaction	IMDELLTRA[a] (N = 252)		Standard of Care (N = 244)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
General disorders and administration site conditions				
Fatigue[c]	39	6	43	10
Pyrexia[d]	29	1.2	11	1.2
Metabolism and nutrition disorders				
Decreased appetite	37	2	23	1.6
Gastrointestinal disorders				
Constipation	30	0.4	22	0
Nausea	25	0.4	32	0
Nervous system disorders				
Dysgeusia[e]	28	0	2.5	0
Headache[f]	16	0	9	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[g]	27	1.6	21	2.5
Respiratory, thoracic and mediastinal disorders				
Cough[h]	17	0	17	0

[a] Graded using CTCAE Version 4.0 and Version 5.0.

[b] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019.

[c] Includes fatigue and asthenia

[d] Includes body temperature increased, hyperthermia, pyrexia

[e] Includes ageusia, dysgeusia, hypogeusia

[f] Includes headache and tension headache

[g] Includes arthralgia, back pain, bone pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain

[h] Includes cough and productive cough

Table 27. FDA - Treatment-emergent AEs Reported in ≥20% of Patients who received Tarlatamab in the Pooled Safety Population (FDA Analysis)

	Tarlatamab (N = 473)	
	All Grades %	Grade 3 or 4 %
Cytokine release syndrome	57	1.9
Fatigue (GT)[a]	48	7
Decreased appetite	38	1.9
Dysgeusia (GT)[b]	34	0
Pyrexia (GT)[c]	33	0.6
Constipation	31	0.4
Musculoskeletal pain (GT)[d]	31	1.9
Nausea	25	1.1

[a] Fatigue (GT) includes PT terms Asthenia, Fatigue
[b] Dysgeusia (GT) includes PT terms Ageusia, Anosmia, Dysgeusia, Hypogeusia
[c] Pyrexia (GT) includes PT terms Body temperature increased, Hyperthermia, Pyrexia
[d] Musculoskeletal pain (GT) includes PT terms Arthralgia, Arthritis, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity, Spinal pain

Laboratory Findings

Data:

In general, clinical laboratory evaluations (eg, serum chemistry, hematology) demonstrated no clinically significant effect of tarlatamab (Section 3 of Module 2.7.4).

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

In the tarlatamab group of Study 20210004, the most frequently reported (> 5% of subjects) shifts of ≥ 3 grades from baseline were decreases in lymphocytes (65 subjects, 26.4%), total neutrophils (24 subjects, 10.1%), sodium (21 subjects, 8.4%), and white blood cells (16 subjects, 6.5%). In the SOC chemotherapy group, the most frequently reported (> 5% of subjects) shifts of ≥ 3 grades from baseline were decreases in total neutrophils (76 subjects, 35.5%), hemoglobin and white blood cells (64 subjects, 28.3% each), lymphocytes (61 subjects, 27%), platelets (45 subjects, 19.9%), and sodium (13 subjects, 5.8%).

In Study 20210004, overall, no subjects in the tarlatamab or SOC chemotherapy group had laboratory values at baseline that potentially met the Hy's Law criteria. One subjects (0.4%) in the tarlatamab group and 2 subjects (0.9%) in the SOC chemotherapy group had laboratory values postbaseline (on study within 30 days) that potentially met the Hy's Law criteria. Further details are provided in Section 12.7 of Study 20210004.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323

The laboratory parameter with ≥ 3 grade change from baseline reported for ≥ 5% subjects treated with any dose of tarlatamab from grade 0 to 3 were decrease in sodium (58 subjects [7.9%]) and decrease in lymphocytes (120 subjects [16.4%]). The laboratory parameter with ≥ 3 grade change from baseline reported for ≥ 5% of subjects treated with tarlatamab 10 mg from grade 0 to 3 were decrease in sodium (26 subjects [5.5%] and decrease in lymphocyte (68 subjects [14.4%]). Overall, for the majority of the laboratory parameters, the subject incidence of shift from grade 0 to grade ≥ 3 was less than 2%.

The incidences of liver function test abnormalities were low across all studies. Increases in AST and ALT were mainly grade 1 and grade 2 and occurred in the setting of CRS (see section 8.2.5.1 Cytokine Release Syndrome). There were no cases that met the Hy`s law criteria of drug-induced liver injury.

The Applicant's Position:

Besides the newly added lymphopenia including lymphocyte count decrease to the ADR table, there were no clinically meaningful or notable trends in laboratory evaluations, and the results were consistent with the known safety profile of tarlatamab.

The FDA's Assessment:

FDA agrees with the Applicant's position. FDA independently verified the Applicant's numbers with regards to laboratory abnormalities from DeLLphi-304. FDA's analysis of selected laboratory abnormalities that worsened from baseline is provided in the table below.

Table 28. FDA - Analysis of Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in DeLLphi-304

Laboratory Abnormality	IMDELLTRA[a] N=252		Standard of care N=244	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Lymphocytes decreased	65	27	62	27
Hemoglobin decreased	51	4.5	86	29
White blood cells decreased	50	7	70	29
Platelets decreased	25	0.4	55	20
Neutrophils decreased[b]	15	10	44	36
Chemistry				
Sodium decreased	57	8	38	7
Potassium decreased	41	4.8	34	4
Aspartate amino transferase increased	40	2.8	29	0.4
Sodium increased	35	0.4	27	0
Alanine aminotransferase increased	32	2	25	0.9
Activated Partial Thromboplastin Time (sec) increased	26	1.3	16	0.9
Creatinine increased	23	0.8	19	0.4
Alkaline phosphate increased	22	0.4	26	1.4

Magnesium decreased	21	0.8	15	1.8
Potassium increased	21	0.8	12	1.8
Creatine Phosphokinase increased	21	1.7	11	0

[a] The denominator used to calculate the rate varied for IMDELLTRA (Range: 229 to 250) and SOC (Range: 205 to 226) based on the number of patients with a baseline value and at least one post-treatment value.

[b] All Grade lab abnormalities occurring at a frequency less than 20% included decreased neutrophils.

In the pooled safety population, The most common (≥ 5%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes (43%), decreased sodium (12%), decreased total neutrophils (9%), and increased uric acid (6%).

Vital Signs

Data:

The assessments of vital signs for the integrated safety analysis set are provided in Section 4 of Module 2.7.4, Summary of Clinical Safety.

No clinically relevant changes were observed in body weight, pulse rate, blood pressure, or body temperature.

The Applicant's Position:

No clinically relevant changes were observed in body weight, pulse rate, blood pressure, or body temperature.

The FDA's Assessment:

A higher proportion of patients had changes in vital signs with tarlatamab treatment compared to SOC. This included patients with higher heart rate (>120 bpm; 12% vs. 6%), higher respiratory rate (>25 breaths/min; 9% vs. 1.2%), higher systolic blood pressure (≥160 mmHg; 27% vs. 6%), lower systolic blood pressure (≤90 mmHg; 21% vs. 10%), higher diastolic blood pressure (≥105 mmHg; 9% vs 1.2%), lower diastolic blood pressure (≤50 mmHg; 16% vs. 10%) and decreased

weight from baseline (≥10%; 19% vs. 10%). A higher number of patients also reported AEs of hypertension (17 vs. 5) and hypotension (14 vs. 7) with tarlatamab compared with SOC. It is of note that the protocol required more frequent assessment of vitals for patients who received tarlatamab compared to standard of care. Five patients had persistent vital sign abnormalities (≥2 abnormal measurements separated by ≥24 hours), including elevated heart rate with concurrent CRS, elevated blood pressure treated with bromazepam, low respiratory rate associated with opioid use for bone pain, and decreased systolic blood pressure with concurrent hypoalbuminemia and urinary tract infection. These persistent abnormalities were attributed to concurrent medical conditions, adverse events like CRS, or concomitant medications with known cardiovascular/respiratory effects. Upon further review, events of vital sign abnormalities appeared transient in nature with a low proportion of patients requiring concomitant medications.

Electrocardiograms (ECGs)

Data:

No clinically relevant changes were observed in electrocardiograms for Studies 20200491 and 20160323 (monotherapy cohorts) only. No statistical analyses of electrocardiogram measurements were performed for Study 20210004.

The Applicant's Position:

No clinically relevant changes were observed in electrocardiograms for Studies 20200491 and 20160323 (monotherapy cohorts) only. No statistical analyses of electrocardiogram measurements were performed for Study 20210004.

The FDA's Assessment:

FDA agrees with the Applicant's position.

QT

Data:

No clinically relevant changes were observed in change from baseline in corrected QT interval by Fridericia (QTcF) and corrected QT interval by Bazett (QTcB) for Studies 20200491 and 20160323 (monotherapy cohorts) only. No statistical analyses of electrocardiogram measurements were performed for Study 20210004.

The Applicant's Position:

No clinically relevant changes were observed in change from baseline in corrected QT interval by Fridericia (QTcF) and corrected QT interval by Bazett (QTcB) for Studies 20200491 and

20160323 (monotherapy cohorts) only. No statistical analyses of electrocardiogram measurements were performed for Study 20210004.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Immunogenicity

Data:

To support this marketing application, immunogenicity was determined by measuring antitarlatamab antibody formation using a validated electro-chemiluminescence-based bridging immunoassay in 3 clinical studies (20160323, 20200491, and 20210004). For study 20200491 and 20210004, samples confirmed to be positive for binding antibodies were subsequently tested in a validated cell-based bioassay to determine neutralizing activity against tarlatamab.

At the clinical regimen of 10 mg Q2W, treatment emergent ADA incidence was 8.5% (20/234) for Study 20210004, 5.6% (7/125) for the Study 20200491, and 8.2% (7/85) for Study 20160323. An analysis of pooled data from all subjects receiving the 10 mg target dose across Studies 20210004, 20200491, and 20160323 showed that 34 of 444 subjects (7.7%) had developed antitarlatamab binding antibodies. In Study 20200491 and 20210004 which employed the neutralizing antibodies assay, the developing neutralizing antibody incidence was 3.1% (11/359 subjects), including 1 from Study 20200491 (1/125; 0.8%) and 10 from Study 20210004 (10/234; 4.3%). Potential impact of antitarlatamab antibodies on the PK, clinical efficacy, and clinical safety of tarlatamab was assessed with the following results:

- Based on inter-subject comparison, tarlatamab peak and trough serum concentrations (central tendency and distribution) are comparable between subjects who were antidrug antibody (ADA) positive at any time during the study and those who were ADA negative over time. Based on the population PK analysis, tarlatamab clearance was estimated to increase by ~14% in subjects who were ADA positive translating to ~ 9% average decrease in Cavg.
- At the clinical dosing regimen, the efficacy measures (including OS, ORR, DCR, and DOR) were similar for antitarlatamab binding antibody positive subjects compared with those who were antitarlatamab antibody negative.
- There was no impact of antitarlatamab antibody development on safety based on assessment of adverse events.

A detailed description of these analyses can be found in the Integrated Summary of Immunogenicity (Module 5.3.5.3).

The Applicant's Position:

Overall, the incidence of antitarlatamab antibody development was low. The development of antitarlatamab antibody did not have clinically relevant impact on tarlatamab PK, efficacy and safety.

The FDA's Assessment:

FDA concurs that the incidence of treatment-emergent ADA in Study 20210004 is 9% and that the combined incidence in Studies 20160323, 20200491, and 20210004 is 8%. The population PK analysis demonstrated an approximately 14% higher clearance in participants with treatment-emergent ADA. Refer to section 6.2.3 for FDA analysis of ADA incidence and impact on drug exposure, efficacy and safety, which determined that the clinical impact of ADA for the dosing regimen of 10 mg Q2W appeared minimal. However, because of the low occurrence of ADA, the labeling states that the effect of these antibodies on the PK, PD, safety and effectiveness of tarlatamab is unknown.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Cytokine Release Syndrome

Data:

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

Incidence of CRS, regardless of Monitoring period: In Study 20210004, 142 (56.3%) subjects in the tarlatamab group and 3 (1.2%) in the SOC chemotherapy group reported any-grade CRS events; CRS incidence in the SOC chemotherapy group occurred after SOC treatment ended and subsequent therapy started. The distribution of events by grade 2 or higher was 13.9% grade ≥ 2, 1.2% grade ≥ 3, and 0.0% grade ≥ 4 in the tarlatamab group. Serious CRS events were reported in 43 (17.1%) subjects in the tarlatamab group. Cytokine release syndrome occurred primarily with the first or second dose of tarlatamab.

Modified Monitoring Period: Similar results were observed in 252 subjects who received tarlatamab in Study 20210004 in which 43 subjects were treated under the 6- to 8-hour monitoring criteria and 209 subjects were treated under the 48-hour monitoring criteria. No subject under the tarlatamab 6- to 8-hour monitoring and 3 (1.4%) subjects under the 48-hour monitoring criteria had grade ≥ 3 CRS events during the first 2 doses. Three (7.0%) subjects under the tarlatamab 6- to 8-hour monitoring criteria and 39 (18.7%) under the 48-hour monitoring criteria had serious CRS events during the first 2 doses. Median time to intervention from last prior tarlatamab administration to first CRS intervention after each dose was 16.6 hours

in subjects under 6- to 8-hour monitoring and 27.3 hours under 48-hour monitoring criteria. The median (95% CI) time to resolution per event (range) was similar in subjects with 6- to 8-hour monitoring (2.0 [NE, NE]; 1-6) and with 48-hour monitoring (2.0 [2.0, 3.0]; 1-28). The outcome (per event) was 'resolved' for most subjects under both criteria (21/21 [100%] with 6- to 8-hour monitoring and 166/169 [98.2%] with 48-hour monitoring).

The rate of hospitalization on cycle 1 day 1 and 8 combined due to any grade treatment-emergent CRS was similar in subjects enrolled under 6- to 8-hour monitoring (3/43 [7.0%] subjects) and 48-hour monitoring (16/209 [7.7%]). One subject under the 48-hour monitoring criteria was hospitalized with a grade ≥ 3 CRS event, and no subject under the 6- to 8-hour monitoring criteria was hospitalized with a grade ≥3 CRS event. Use of CRS interventions was similar in subjects under 6- to 8-hour monitoring (9 [20.9%] subjects) and 48-hour monitoring (45 [21.5%]). Corticosteroids were the most common intervention, used by 20.9% of subjects under 6- to 8-hour monitoring and 15.3% of subjects under 48-hour monitoring criteria. Tocilizumab was used by 2.3% with 6- to 8-hour monitoring and 3.8% with 48-hour monitoring. Hospital-required interventions, such as vasopressor administration and high-flow oxygen, were rarely required, each required in 1 subject (0.4%).

Overall, in Study 20210004, the 6- to 8-hour monitoring criteria approach did not alter the established CRS profile of tarlatamab including frequency, severity, time to intervention, time to resolution, and outcome.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323

Incidence of CRS, regardless of Monitoring period: Using the Amgen MedDRA Query (AMQ) narrow search, across all studies in the integrated analysis, CRS adverse events of any grade were reported in 268 subjects (56.7%) receiving tarlatamab 10 mg. The distribution of events by severity was 17.3% grade ≥ 2, 1.9% grade ≥ 3, and 1 (0.1%) grade 4. With tarlatamab 10 mg, serious CRS events were reported for 93 subjects (19.7%), and 3 subjects (0.6%) had a CRS event that led to treatment discontinuation; no CRS event was fatal. Cytokine release syndrome occurred primarily with the first or second dose of tarlatamab. Overall, CRS interventions including tocilizumab, vasopressors, and IV fluid were used by 26 (5.5%), 2 (0.4%), and 34 (7.2%) subjects receiving tarlatamab 10 mg, respectively.

Incidence of CRS events for the subjects who received any dose of tarlatamab in the integrated analysis (730 subjects) were similar to those who received tarlatamab 10 mg (473 subjects).

Modified Monitoring Period: Results for the integrated analysis were similar to those seen with Study 20210004. In the integrated analysis, during the first 2 doses of tarlatamab 10 mg, CRS rates were comparable under 6- to 8-hour and 24- to 48-hour monitoring criteria (46.6% and 57.3%, respectively). No grade ≥ 3 or 4 events were reported in subjects under 6- to 8-hour monitoring criteria; and 7 (1.8%) and 1 (0.3%) subjects reported grade ≥ 3 and ≥ 4 events under 24- to 48-hour monitoring. No fatal events were reported in subjects with either of the

monitoring criteria. Serious adverse events were reported in 8 subjects (11.0%) with 6- to 8-hour and 79 subjects (19.8%) with 24- to 48-hour monitoring criteria. The outcome (per event) was 'resolved' for most subjects under both criteria, with a total of 6 subjects (1.3%) overall with an unresolved CRS event (all under 24- to 48-hour monitoring). The median (95% CI) time to resolution per event was similar in subjects under 6- to 8-hour monitoring (2.0 [2, 3]) and 24- to 48-hour monitoring criteria (3.0 [NE, NE]).

The most common intervention used for CRS was tocilizumab, used in 23 of 400 subjects (5.8%) with 24- to 48-hour monitoring and in 1 subject (1.4%) with 6- to 8-hour monitoring. Hospital-required interventions, such as vasopressor administration, were rarely required (2 subjects [0.4%] overall).

Overall, in the integrated analysis, the 6- to 8-hour monitoring criteria approach did not alter the established CRS profile of tarlatamab including severity, time to intervention, time to resolution, and outcome.

The Applicant's Position:

Overall, CRS in subjects treated with tarlatamab is generally low grade in nature, rarely escalating to require high-acuity interventions, and occurs almost exclusively after the first 2 infusions of tarlatamab with few grade 2 and higher events reported from cycle 1 day 15 and beyond. The monitoring period does not impact the frequency, grade, severity, time to intervention, duration, or time to resolution of CRS events. Given the predictable CRS profile and the rare requirement for high acuity interventions, hospital-based monitoring for CRS is not required for tarlatamab.

The FDA's Assessment:

FDA performed independent analysis of the CRS events from the pooled dataset of patients who received tarlatamab 10 mg from DeLLphi-300, DeLLphi-301, DeLLphi-304 and confirms the Applicant's numbers. Overall, in the pooled population, CRS occurred in 57% of patients, with 39% of patient experiencing grade 1 CRS, 15% of patients experiencing grade 2 CRS, 8 patients (1.7%) experiencing grade 3 CRS and 1 patient experiencing grade 4 CRS (0.2%). Recurrent CRS occurred in 24% of patients treated with tarlatamab, including 20% Grade 1 and 3.4% Grade 2; one patient experienced recurrent Grade 3 CRS.

Among the 268 patients who experienced CRS, 73% had CRS after the first dose, 60% had CRS after the second dose, and 15% had CRS following the third or later dose. Following the Cycle 1 Day 1, Day 8, Day 15 infusions, 24%, 8%, and 1% of patients experienced Grade $\geq$ 2 CRS, respectively. From Cycle 2 onwards, 1.5% of patients experienced Grade $\geq$ 2 CRS. Of the patients who experienced CRS, 31% received steroids and 10% required tocilizumab. The

median time to onset of all grade CRS from most recent dose of tarlatamab was 16 hours (range: start of infusion to 15 days). The median time to onset of Grade ≥ 2 CRS from most recent dose of tarlatamab was 15 hours (range: start of infusion to 15 days).

(b) (4)

Of note, 24 to 48 hour monitoring consisted of data from the DeLLphi-300, DeLLphi-301, DeLLphi-304 trials, 6 to 8 hour monitoring consisted of data from the DeLLphi-300 and DeLLphi-304 trials while 1 to 2 hour monitoring consisted of data from the ongoing DeLLphi-305 (Study 20200041) and DeLLphi-306 trials (Study 20230016). In addition, data from Study 20230273 (n=31) with 6 to 8 hour monitoring for CRS was not pooled with the 6 to 8 hour monitoring data as this study was conducted from patients in a single region (China). The study reported an 87% CRS incidence with no Grade ≥3 CRS events, only one patient having an AE leading to dose interruption and no patients having AEs leading to discontinuation.

Table 29. FDA - Analysis of Treatment-emergent CRS Data Across Different Monitoring Periods in Tarlatamab Development Program

	24 to 48 hour monitoring (N = 400)	6 to 8 hour monitoring (N = 73)	1 to 2 hour monitoring (N = 346)
CRS Incidence	58%	48%	37%
Grade 3 CRS	2%	1.4%	0.3%
Grade 4+ CRS	0.3%	0	0
Serious TEAEs CRS	21%	12%	12%
CRS leading to discontinuation	0.8%	0	0.3%
CRS leading to treatment delay	2.5%	0	2.6%
Median time to event from first dose (hours)	15	14	Not reported
Median time to resolution (days)	3	2	Not reported

	24 to 48 hour monitoring (N = 400)	6 to 8 hour monitoring (N = 73)	1 to 2 hour monitoring (N = 346)
CRS treatments	6% tocilizumab, 17% steroids, 8% IV fluid bolus, 0.5% vasopressors	2.7% tocilizumab, 22% steroids, 6% IV fluid bolus, 0% vasopressors	3.4% tocilizumab, 15% steroids, 3.2% IV fluid bolus, 0.6% vasopressors
Proportion of event resolution	99%	100%	98%

Table 30. FDA - Time from Last Prior Tarlatamab Administration to First CRS by Dose

	24 to 48 hour monitoring (N = 400)	6 to 8 hour monitoring (N = 73)
Cycle 1 Day 1		
Number of patients with CRS	172	24
0 to ≤8 hours	31%	33%
>8 to ≤16 hours	36%	29%
>16 to ≤24 hours	8%	8%
>24 hours	20%	8%
Missing	5%	21%
Cycle 1 Day 8		
Number of patients with CRS	140	21
0 to ≤8 hours	5%	5%
>8 to ≤16 hours	19%	19%
>16 to ≤24 hours	21%	29%
>24 hours	49%	24%
Missing	5%	23%

Overall, when comparing CRS data across monitoring periods, the summary statistics appear similar to each other. FDA considered data provided for patients with 1 to 2 hour monitoring as incomplete as these trials are ongoing and the time to onset of CRS was not reported. In addition,

(b) (4), and it is possible that differences in the study populations in these trials, such as potential for lower tumor burden, might impact the incidence of CRS.

When reviewing data from patients who had 6 to 8 hour monitoring compared to 24 to 48 hour monitoring, the reported incidence of CRS was slightly lower in the 6 to 8 hour monitoring group (48%) compared with the 24 to 48 hour monitoring group (58%), with low rates of grade ≥3 AEs and AEs leading to delays and discontinuations for both monitoring periods. In addition, the median time to event, time to resolution and proportion of resolved events were similar between each monitoring period. However, only 19% of patients had CRS events with onset within 8 hours from last prior tarlatamab administration and approximately 25% of the time to onset data was missing for patients who had 6 to 8 hour monitoring. Furthermore, an FDA review of tarlatamab postmarketing data initiated by the Division of Pharmacovigliance identified 240 cases of grade ≥2 CRS. While the majority of events were grade 2 (76%), 16% were grade 3, 6% grade 4 and 1.7% grade 5, representing an increased proportion of higher grade events relative to what has been reported in clinical trials. (b) (4)

8.2.5.2 Immune Effector Cell-associated Neurotoxicity Syndrome and Associated Neurological Events

Data:

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

Using the AMQ broad search, 8.3% and 5.7% in the tarlatamab and SOC groups, respectively, had events of ICANS and associated neurological events. Using the preferred term of ICANS, 15 (6.0%) subjects in the tarlatamab group and 2 (0.8%) in the SOC chemotherapy group had any-grade ICANS. Grade ≥ 3 ICANS and associated neurologic events were reported in 1 subject (0.4%) in the tarlatamab group which started with grade 1 ICANS and progressed to grade 3 and then grade 5. Due to the presence of significant confounding factors, including 2 episodes of grade 3 pneumonia, it was concluded that pneumonia, rather than CRS or ICANS, was the likely cause of fever, hypotension, subsequent encephalopathy, and death. Grade ≥ 3 ICANS and associated neurologic events were reported in 4 subjects (1.6%) in the SOC chemotherapy group.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323

At the tarlatamab 10 mg dose across the studies, ICANS and associated neurological events were reported for 11.2% of subjects. Using the preferred term of ICANS, 4.7% had any-grade

ICANS. Grade ≥ 2 and ≥ 3 events (broad search) were reported for 5.1% and 0.8%, respectively. Grade ≥ 4 and fatal events were each reported for 2 subjects (0.4%). Two subjects (0.4%) had ICANS events leading to treatment discontinuation: 1 due to ICANS and 1 due to muscular weakness (single instance, grade 2, nonserious, without concurrent neurological symptoms).

The Applicant's Position:

ICANS is an important identified risk for tarlatamab. The incidence of ICANS and associated neurological events in Study 20210004 including serious events was higher in the tarlatamab group than in the SOC chemotherapy group and similar with that seen in the integrated analysis. The incidence was consistent with the known ICANS profile of tarlatamab. Most of the events of ICANS and associated neurological events based on AMQ broad search were low grade (grade 1 or 2). The majority of cases reporting preferred terms other than ICANS did not meet the case definition of ICANS.

The FDA's Assessment:
FDA generally agrees with the Applicant's position. ICANS occurred in 10% of patients treated with tarlatamab in the pooled safety dataset, including with one fatal event. The preferred terms included ICANS (4.7%), muscular weakness (3.2%), cognitive disorder (0.6%), aphasia (0.6%), depressed level of consciousness (0.4%), seizures (0.4%), encephalopathy (0.4%), and leukoencephalopathy (0.2%). There was one fatal reaction of ICANS. Recurrent ICANS occurred in 1.5% of patients. Of the patients who experienced ICANS, most experienced the event following Cycle 1 Day 1 (2.5%) and Cycle 1 Day 8 (3.6%). Following Day 1, Day 8, and Day 15 infusions, 1.3%, 1.3% and 0.4% of patients experienced ≥ Grade 2 ICANS, respectively. The median time to onset of ICANS from the first dose of tarlatamab was 16 days (range: 1 to 862 days). The median time to resolution of ICANS was 4 days (range: 1 to 40 days).

8.2.5.3 Neurological Events

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

A total of 140 subjects (55.6%) in the tarlatamab group and 86 subjects (35.2%) in the SOC chemotherapy group had neurological events based on the nervous system disorders and psychiatric disorders system organ classes. The most frequently reported (≥ 5% of subjects) neurological events in the tarlatamab group were dysgeusia (24.2%), headache (15.1%), dizziness (9.5%), insomnia (7.1%), and ICANS (6.0%). In the SOC chemotherapy group, the most frequently reported events were dizziness (10.2%) and headache and insomnia (8.6% each). Nine (3.6%) and 14 subjects (5.7%) had grade ≥ 3 neurological events, 16 (6.3%) and 10 subjects (4.1%) had serious neurological events, and 3 (1.2%) and 4 subjects (1.6%) had neurological events leading to investigational product discontinuation in the tarlatamab and SOC chemotherapy groups, respectively. Of note, dysgeusia (24.2% in tarlatamab and 1.6% in SOC chemotherapy) is included in neurological events. One subject (0.4%) in the tarlatamab group had a fatal neurological event of ICANS.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323

Of 473 subjects overall, neurological events were reported for 304 (64.3%); neurological events were considered related to tarlatamab for 370 subjects (50.7%). Grade ≥ 2 and grade ≥ 3 neurological adverse events were reported for 148 (31.3) and 31 (6.6%), respectively. Grade ≥ 4 neurological events were reported for 6 (1.3%). Serious adverse neurological events were reported for 38 (8.0%). Fatal events were reported for 2 subjects (0.4%); preferred terms were ICANS and seizure in the respective subjects. Six subjects (1.3%) had neurological events leading to treatment discontinuation.

The median (Q1, Q3) time to first onset of neurological events from the first dose of tarlatamab was 13.0 (1, 785) days for any grade, 22.0 (1, 581) days for grade ≥ 2, and 61.0 (1, 414) days for grade ≥ 3. The median (Q1, Q3) time to first onset of neurological events from the last prior dose of tarlatamab was 3.0 (1.0, 8.0) days for any grade, 4.0 (2.0, 9.0) days for grade ≥ 2, and 5.0 (2.0, 14.0) days for grade ≥ 3 neurological events. The median (Q1, Q3) duration of resolved neurological events was 8.0 (2.0, 28.0) days for any grade, 7.0 (2.0, 28.0) days for grade ≥ 2, and 4.0 (1.5, 16.5) days for grade ≥ 3, as of the data cutoff date. The Kaplan-Meier median (95% CI) time to resolution was 66.0 (43.0, 114.0) days for any grade, 42.0 (20.0, 74.0) days for grade ≥ 2, and 14.0 (4.0, 38.0) days for grade ≥ 3 neurological events.

The Applicant`s position:

Overall, neurological events in Study 20210004 were predominantly low grade and led to few treatment discontinuations. The most common neurological events were dysgeusia and headache, with dysgeusia accounting for a significant number of the events in the tarlatamab group. The most common serious neurological event was ICANS. The incidence of neurological events in Study 20210004 was comparable with the integrated analysis and known safety profile of tarlatamab.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. In the pooled safety population, neurological events occurred in 65% of patients, with grade 3 or higher events in 7% of patients including fatal events in 0.2%. The most frequent neurologic toxicities were dysgeusia (34%), headache (17%), peripheral neuropathy (9%), dizziness (9%), and insomnia (8%).

8.2.5.4 Hepatotoxicity

The FDA's Assessment:

In the pooled safety population, based on laboratory data, elevated ALT occurred in 39% of patients who received tarlatamab, including 2.5% Grade 3 or 4. Elevated AST occurred in 43% of patients, including 3.2% Grade 3 or 4. Elevated bilirubin occurred in 16% of patients, including 1.3% Grade 3 or 4.

8.2.5.5 Neutropenia

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

Neutropenia EOIs (AMQ narrow search) were reported for 52 subjects (20.6%) in the tarlatamab group and 124 subjects (50.8%) in the SOC chemotherapy. Grade ≥ 2 and grade ≥ 3 neutropenia events were reported for 45 subjects (17.9%) and 30 subjects (11.9%), respectively, in the tarlatamab group and 116 subjects (47.5%) and 96 subjects (39.3%), respectively, in the SOC chemotherapy group. Grade ≥ 4 neutropenia events were reported for 11 subjects (4.4%) in the tarlatamab group and 46 subjects (18.9%) in the SOC chemotherapy group; no fatal events were reported in the tarlatamab group and 1 fatal event was reported in the SOC chemotherapy group. A total of 7 subjects (2.8%) in the tarlatamab group and 32 subjects (13.1%) in the SOC chemotherapy group had serious neutropenia events, and no subjects in the tarlatamab group and 2 subjects (0.8%) in the SOC chemotherapy group had neutropenia events leading to IP treatment discontinuation. Neutropenia events were considered by the investigator as related to IP for 34 subjects (13.5%) in the tarlatamab group and 119 subjects (48.8%) in the SOC chemotherapy group.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323

Of 473 subjects overall, neutropenia events were reported for 87 subjects (18.4%); neutropenia events considered treatment-related in 62 subjects (13.1%). Grade ≥ 2 and grade ≥ 3 neutropenia adverse events were reported for 46 subjects (9.7) and 16 subjects (3.4%), respectively. Grade ≥ 4 neutropenia events were reported for 16 subjects (3.4%). Serious adverse neutropenia events were reported for 11 subjects (2.3%). No fatal events or events leading to treatment discontinuation were reported. The most frequently reported (≥ 2% of subjects) neutropenia events were neutropenia (49 subjects [10.4%]) and neutrophil count decreased (31 subjects [6.6%]).

The median (Q1, Q3) time to first onset of neutropenia events from the first dose of tarlatamab was 42.0 (3, 344) days for any grade, 48.0 (3, 344) days for grade ≥ 2, and 46.5 (14, 344) days for grade ≥ 3. The median (Q1, Q3) time to first onset of neutropenia events from the last prior dose of tarlatamab was 14.0 (3.0, 15.0) days for any grade, 14.0 (5.0, 17.0) days for grade ≥ 2, and 15.0 (14.0, 29.0) days for grade ≥ 3 neutropenia events. The median (Q1, Q3) duration of resolved neutropenia events was 9.0 (4.0, 15.0) days for any grade, 8.0 (4.0, 14.0) days for grade ≥ 2, and 5.0 (3.0, 8.0) days for grade ≥ 3, as of the data cutoff date. The Kaplan-Meier

median (95% CI) time to resolution was 11.0 (8.0, 14.0) days for any grade, 8.0 (6.0, 12.0) days for grade≥ 2, and 6.0 (4.0, 8.0) days for grade ≥ 3 neutropenia.

The Applicant`s position:

Neutropenia incidence was higher in the SOC chemotherapy group compared with the tarlatamab group in Study 20210004. The majority of neutropenia events were nonserious. Overall, the incidence of neutropenia cases in phase 3 Study 20210004 were consistent with the integrated safety summary data and the known neutropenia profile of tarlatamab.

The FDA's Assessment:

FDA agrees with the Applicant's position. In the pooled safety population, based on laboratory data, decreased neutrophils occurred in 16% of patients, including 9% Grade 3 or 4. The median time to onset for Grade 3 or 4 decreased neutrophil count was 41 days (range: 2 to 306 days).

8.2.5.6 Hypersensitivity

Data:

Tarlatamab Versus Standard of Care Chemotherapy in Study 20210004

Based on the SMQ narrow search, hypersensitivity/anaphylactic reactions EOIs were reported for 36 subjects (14.3%) in the tarlatamab group and 28 subjects (11.5%) in the SOC chemotherapy. Grade ≥ 2 hypersensitivity events (SMQ narrow search) were reported for 16 subjects (6.3%) in the tarlatamab group and 10 subjects (4.1%) in the SOC chemotherapy group. One subject (0.4%) in the tarlatamab group had a fatal event of "circulatory collapse" which was captured under hypersensitivity MedDRA term, and no other subject had grade 3 or higher events in this group; the investigator considered the event unrelated to the investigational product and considered the death event more likely to be a cardiovascular event [e.g., stroke]). In the tarlatamab group, serious hypersensitivity events and hypersensitivity events leading to investigational product treatment discontinuation were reported in 2 subjects (0.8%) each. In the SOC chemotherapy group, no subject had grade ≥ 3 hypersensitivity events, fatal events, serious hypersensitivity events, or hypersensitivity events leading to investigational product treatment discontinuation. Hypersensitivity events were considered by the investigator as related to investigational product for 27 subjects (10.7%) in the tarlatamab group and 13 subjects (5.3%) in the SOC chemotherapy group. Overall, the majority of the adverse events were non-serious and there were no clinically significant differences between tarlatamab and SOC chemotherapy.

Integrated Safety Analysis of Tarlatamab 10 mg Q2W in Studies 20210004, 20200491, and 20160323

Of 473 subjects overall, hypersensitivity events (SMQ narrow) were reported for 65 subjects (13.7%); hypersensitivity events were considered related to tarlatamab for 43 subjects (9.1%). Grade ≥ 2 and grade ≥ 3 hypersensitivity adverse events were reported for 24 subjects (5.1) and 4

(0.8)%), respectively. Grade ≥ 4 hypersensitivity events were reported for 1 subject (0.2%). Serious adverse hypersensitivity events were reported for 3 subjects (0.6%). Fatal events were reported for 1 subject (0.1%) (which had initially progressed from grade 3 hypersensitivity events to grade 4 events and then to fatal events); the preferred term was circulatory collapse. Two subjects (0.4 %) had hypersensitivity events leading to treatment discontinuation. The most frequently reported (≥ 2% of subjects) hypersensitivity adverse events were rash (34 subjects [7.2%]).

The median (Q1, Q3) time to first onset of hypersensitivity events from the first dose of tarlatamab was 42.0 (3, 344) days for any grade, 48.0 (3, 344) days for grade ≥ 2, and 46.5 (14, 344) days for grade ≥ 3. The median (Q1, Q3) time to first onset of hypersensitivity events from the last prior dose of tarlatamab was 2.5 (1.0, 9.5) days for any grade, 3.5 (1.0, 10.5) days for grade ≥ 2, and 7.5 (4.5, 14.0) days for grade ≥ 3 hypersensitivity events. The median (Q1, Q3) duration of resolved hypersensitivity events was 7.0 (3.0, 21.0) days for any grade, 5.0 (1.0, 28.0) days for grade ≥ 2, and 4.0 (3.0, 434.0) days for grade ≥ 3, as of the data cutoff date. The Kaplan-Meier median (95% CI) time to resolution was 13.0 (5.0, 17.0) days for any grade, 16.0 (3.0, 87.0) days for grade ≥ 2, and 4.0 (3.0, NE) days for grade ≥ 3 hypersensitivity events.

The Applicant`s position:

Overall, results were comparable between tarlatamab 10 mg and SOC chemotherapy in Study 20210004. Across both datasets (Study 20210004 and integrated analysis), the majority of hypersensitivity adverse events were nonserious (grade 1 or 2) and most resolved without intervention or medication. Hypersensitivity remains as a potential risk and will continue to be monitored as an event of interest. It is already included in core labeling under Warnings and Precautions.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.5.7 Other Submission-Specific Safety Issues

FDA Assessment: Additional submission-specific safety issues relevant to the product labeling included other cytopenias and infections.

In the pooled safety population, based on laboratory data, decreased platelets occurred in 30%, including 2.2% Grade 3 or 4. The median time to onset for Grade 3 or 4 decreased platelets was 67 days (range: 3 to 420 days). Decreased hemoglobin occurred in 56% of patients, including 4.7% Grade 3 or 4.

Febrile neutropenia was reported as an adverse event in 1.5% of patients treated with IMDELLTRA.

In the pooled safety population, infections including opportunistic infections occurred in 43% of patients who received tarlatamab, including 14% Grade 3 or 4. The most frequent infections were pneumonia (11%), urinary tract infection (9%), COVID-19 (6%), upper respiratory tract infection (4.7%), respiratory tract infection (4%), candida infection (2.1%), oral candidiasis (2.1%) and nasopharyngitis (2.1%).

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

Patient Patient-reported outcomes are discussed in Efficacy Results – Secondary and other relevant endpoints.

The Applicant's Position:

Patient-reported outcomes are discussed in Efficacy Results – Secondary and other relevant endpoints.

The FDA's Assessment:

See FDA description and analyses of patient-reported outcomes in Section 8.1.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Summaries of adverse events and treatment-related adverse events; subject incidence of adverse events and treatment-related adverse events by preferred term; and subject incidence of adverse events and treatment-related adverse events by system organ class were analyzed by intrinsic and extrinsic factor subgroups of race (Asian, Black or African American, White, Other), age (< 65 years versus ≥ 65 years), and sex (men, women).

Overall summaries of adverse events by subgroup are provided in Section 5.1 and Section 5.2 of Module 2.7.4, SCS. In the integrated monotherapy analysis set, no notable safety trends were observed across the subgroups examined. No meaningful differences were observed in the types of adverse events or treatment-related adverse events reported in the subgroups examined; however, small sample sizes in some subgroups limit the ability to draw meaningful conclusions.

The Applicant's Position:

Overall, subgroup analyses demonstrated a pattern of events (types of adverse events or treatment-related adverse events) consistent with that reported for the overall study population.

The FDA's Assessment:

FDA agrees with the Applicant's position. From FDA review, there were no new safety signals identified or clinically meaningful differences in safety reported between demographics subgroups (age, race, sex and region) in the pooled safety dataset. The Geriatric Use section of product labeling includes the following statement: "Of the 473 patients with SCLC who received IMDELLTRA 10 mg as a single agent, 51% were 65 years of age or older and 11% were 75 years of age or older. No overall differences in IMDELLTRA pharmacokinetics, safety or efficacy were observed between older patients (≥ 65 years of age) and younger patients."

8.2.8. Specific Safety Studies/Clinical Trials

Data:

Not applicable as no studies were conducted to evaluate a specific safety concern.

The Applicant's Position:

Not applicable

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

Not Applicable.

The Applicant's Position:

See Pharmacology/Toxicology review.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

Data:

No clinical studies of tarlatamab have been conducted in pregnant or breastfeeding women. No breastfeeding cases were reported with exposure to tarlatamab.

There are no clinical studies to evaluate the effect of tarlatamab on fertility.

The Applicant's Position:

There are no available data from the use of tarlatamab in pregnant women. Based on its mechanism of action, tarlatamab may cause fetal harm when administered to a pregnant woman.

There are no clinical studies to evaluate the effect of tarlatamab on fertility.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth

Data:

Not Applicable.

The Applicant's Position:

Safety and effectiveness of tarlatamab in pediatric patients have not been established. Given that the molecular target of tarlatamab, delta-like ligand 3 (DLL-3), was moved to the nonrelevant molecular target list leading to waiver, FDA Reauthorization Act of 2017 requirements no longer apply, and given tarlatamab's orphan drug designation, Amgen is exempt from the requirements of the Pediatric Research Equity Act.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

There is no clinical experience with overdose with tarlatamab. Doses up to 100 mg Q2W and 200 mg Q3W have been administered in clinical trials. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

The Applicant's Position:

See above.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

As of 15 November 2024, Amgen received a total of 489 adverse drug reactions cumulatively from medically confirmed and unconfirmed spontaneous sources, 284 of 489 were serious and 205 were nonserious (Section 6.3 of Periodic Benefit Risk Evaluation Report [PBRER] No. 01). As of 15 November 2024, Amgen received a total of 53 serious adverse reactions cumulatively from noninterventional postmarketing sources and other solicited sources.

Cytokine release syndrome, ICANS, and neutropenia were important identified risks for tarlatamab. Cumulatively, 170 cases with 240 events of CRS (156 serious, 84 nonserious) were reported from postmarketing sources. Of these 170 cases, 154 cases were medically confirmed. Five events had a fatal outcome (Table 16 of PBRER No. 01). During the reporting period and cumulatively, 64 cases with 65 events of ICANS (64 serious, 1 nonserious) were received from postmarketing sources. Of these 64 cases, 57 cases were medically confirmed (Table 18 of PBRER No. 01). One case had a fatal event outcome (see Section 16.3.2.2 of PBRER No. 1 for details). For neutropenia, during the reporting period and cumulatively, 3 cases with 3 serious events were received from postmarketing sources. All these 3 cases were medically confirmed, and no events with fatal outcome were reported. The review of information from clinical trials and postmarketing sources and cumulative review of safety information from clinical trials and postmarketing sources did not provide significant new insights or highlight new concerns for the important identified risk of CRS, ICANS, and neutropenia. Amgen will continue to monitor these risks through routine PV activities.

The Applicant's Position:

(b) (4)

Cumulatively, since the International Birth Date of tarlatamab up to the end of the PBRER No. 01 reporting period, there was an estimated (b) (4) of exposure to tarlatamab in the marketed setting.

During the reporting period of PBRER No. 01, no new benefit data became available, and the evaluation of safety data did not result in the detection of any new risks for tarlatamab. Therefore, the overall benefit-risk profile of tarlatamab remains favorable for the approved indication.

The FDA's Assessment:

FDA reviewed data from the PBRERs provided thus far with tarlatamab. Overall, there were 13 cases of fatal CRS noted. In addition, there were 14 cases of grade 4 CRS. Given there has been only one case of Grade ≥4 CRS described in the datasets provided in this supplement, it appears there may be a higher rate of grade 4 CRS in the postmarketing setting. This is not unexpected given that clinical trial patients must meet more stringent eligibility criteria than patients treated in the postmarketing setting. Summaries of the cases of fatal CRS are provided below. Of the cases described, FDA could not definitively exclude tarlatamab contributing to the patient's death.

- Case 1: FAERS Case # 24375138, Expedited Report, Spontaneous, USA An elderly male of unspecified age was treated with tarlatamab for ES-SCLC. He had a poor Eastern Cooperative Oncology Group performance status at the time of treatment initiation. No historical medical conditions, prior treatments, or concomitant medications were reported. Following the first dose of tarlatamab, he developed CRS at an unspecified time. He was subsequently admitted to the intensive care unit (ICU) and died due to complications from CRS. No treatments or interventions were reported. No further details were provided.
- Case 2: FAERS Case # 24868219, Expedited Report, Clinical Study, USA A 63-year-old male was treated with tarlatamab for small cell prostate cancer with bone metastases (off-label indication) as part of an individual patient use program. His medical history included hypertension, hyperlipidemia, sleep apnea, type II diabetes, transient ischemic attacks, aortic stenosis, chronic kidney disease. Previous treatments included androgen deprivation therapy with bicalutamide, abiraterone, enzalutamide, combination carboplatin + etoposide + durvalumab followed by durvalumab monotherapy, and carboplatin + cabazitaxel. The patient was admitted to the hospital for the first dose of tarlatamab. His pre- and post-infusion vital signs were normal. However, four hours later he experienced hypotension progressing to grade 4 CRS with fever and worsening hypoxia over the next four hours. He required 12 liters of oxygen supplementation. He

had concurrent ICANS. A chest X-ray showed no acute cardiopulmonary abnormality. He was treated with tocilizumab and dexamethasone. Subsequently, there was difficulty obtaining a pulse oximetry reading and rapid response was called. His extremities appeared cyanotic and were cold to the touch. He was placed on continuous positive airway pressure. A fluid bolus was administered. Overnight, his fever worsened to 102.8°F. He was further treated with intravenous (IV) methylprednisolone and oral levetiracetam. Subsequently, he experienced a cardiac arrest requiring cardiopulmonary resuscitation, epinephrine, and intubation. Ventricular fibrillation was noted. Amiodarone and bicarbonate were administered. The patient's family requested cessation of cardiopulmonary resuscitation, and the patient died due to complications of CRS. Blood cultures remained negative after five days.

- Case 3: FAERS # 24428790, Expedited Report, Clinical Study, South Korea A 72-year-old male was treated with tarlatamab for ES-SCLC as part of an individual patient use program. Prior treatment for SCLC was not specified. His medical history included ursodeoxycholic acid-induced hepatitis, diabetes mellitus, radiation pneumonitis, coronary artery disease with prior percutaneous coronary intervention. He had no relevant concomitant medications. His vital signs were normal pre- and post-tarlatamab step-up dose. However, he experienced grade 2 CRS approximately eight hours later based on a fever and hypoxia requiring 3 L of supplemental oxygen via nasal prong. He was treated with tocilizumab and high-dose steroids. Concurrently, he experienced grade 4 ICANS. Over the next two days, he developed tumor lysis syndrome (TLS) and progressively increasing liver enzymes followed by continued clinical deterioration requiring vasopressors, adenosine, rasburicase, platelets, and antibiotics. He died four days after initiating tarlatamab due to complications of CRS, ICANS, and TLS.
- Case 4: Manufacturer Control # KORNI2025053857, Spontaneous Report, South Korea A 69-year-old female was treated with tarlatamab for ES-SCLC as part of an individual patient use program. The patient had extensive metastatic disease involving the liver, peritoneum, lymph nodes, and lungs. Imaging showed hepatomegaly with multiple heterogeneous hepatic lesions, mild peritoneal thickening, ascites, and suspected peritoneal carcinomatosis. She had no relevant concomitant medications. The patient tolerated the step-up tarlatamab dose and received the full 10 mg dose on cycle 1, day 8, despite mild liver enzyme elevations and a low platelet count (54x103/µL). The following day, the patient experienced grade 4 CRS, metabolic acidosis (pH 6.997), hepatic failure, and coagulopathy (International Normalized Ratio: 5.63). She was treated with tocilizumab, steroids, vasopressors, and high-flow supplemental oxygen. However, her condition progressively worsened, and she developed multiorgan failure and suspected pneumonia. Tarlatamab therapy was discontinued, and she transitioned to palliative care. She died twelve days after initiating tarlatamab. The investigator confirmed CRS as the likely cause of death, and ruled out septic shock because there was no clear evidence of infection despite empiric antibiotic administration.

- Case 5: USASP2025159868 - Literature-Based Cluster Case This case described a cluster of patients who experienced serious immune-related adverse events while receiving tarlatamab, based on a publication titled "Tarlatamab-induced immune-related adverse events: retrospective real-world pharmacovigilance study using FAERS database" by Vojjala et al. (2025). The case lacked comprehensive patient information, as past medical history, prior procedures, prior anti-cancer therapies, and concomitant medications were not reported. Patients were exposed to tarlatamab on unknown dates with no details regarding dose, frequency, route, or duration of administration provided. The literature source indicated that adverse events included CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), non-ICANS neurotoxicity, and other unspecified adverse events. A total of 185 adverse events were associated with tarlatamab exposure, with CRS being the most frequently reported event (n=73, 39.4%), followed by ICANS (n=48, 25.9%) and non-ICANS neurotoxicity. Among patients with CRS, 28% (n=21) were hospitalized and 25% (n=7) of them died, while among those with ICANS, 35.4% (n=17) required hospitalization and 23.5% (n=4) died. Overall, CRS was associated with 8% mortality and ICANS with 9% mortality. Deaths occurred on unknown dates in association with CRS, ICANS, non-ICANS neurotoxicity, and other adverse events, with no autopsy details reported. The reporter assessed the events as possibly related to tarlatamab. Amgen's assessment noted that causality could not be established due to missing critical information including appropriate tarlatamab dosing with step dosing, onset dates of CRS events, clinical courses, and treatment details, as well as lack of patient medical history and concomitant therapy information essential for evaluating contributing factors to the deaths.
- Case 6: (b) (6) An 83-year-old male patient with ES-SCLC whose past medical history and prior anti-cancer therapies were not reported. The patient's current medical condition included lung and brain metastases and aortic stenosis. On (b) (6), the patient was hospitalized due to metastatic SCLC, and on (b) (6), he received the first and only dose of tarlatamab 1 mg/kg (noted as off-label use) following premedication with dexamethasone. Within hours of the first infusion, the patient reported fever, hypotension, and dyspnea. Approximately 22 hours after the first infusion, the patient developed grade 1 fever and rigors and was transferred to the intensive care unit, where cultures were taken and treatment with piperacillin/tazobactam was initiated. At (b) (6), the patient developed hypoxia and received tocilizumab, followed two hours later by dyspnea managed with dexamethasone and supplemental oxygen (2 L/min). The patient subsequently developed respiratory failure requiring intubation and was diagnosed with grade 4 CRS. Treatment included 3 doses of tocilizumab, pulse corticosteroids, and anakinra for 7 days, but despite these measures, the patient remained intubated as of (b) (6). On an unspecified date, the patient also reported arthralgia and pain in the hip (associated with a prior fall), cough, and pneumonitis. On (b) (6), the patient died due to pneumonitis, metastatic SCLC, and CRS, with no autopsy performed. Amgen's assessment noted that while CRS was

considered related to tarlatamab by the investigator, the fatal outcome was confounded by ongoing underlying disease progression with lung and brain metastasis present at baseline, and the case lacked details regarding pneumonitis, medical history, and concomitant therapy. Additionally, the reported tarlatamab dose of "1 mg/kg, off label use" was inconsistent with approved product labeling, prompting a query for dose confirmation.

- Case 7: (b) (6) Serious, Spontaneous Report This concerned a 66-year-old male patient with a history of SCLC and multiple prior chemotherapy regimens including carboplatin, etoposide, durvalumab, and amrubicin. The patient's current medical condition included type 2 diabetes mellitus, hypertension, metastases to liver and lymph nodes, and elevated hepatic enzyme levels. Tarlatamab was initiated as third-line therapy on (b) (6), at a dose of 1 mg, with prophylactic corticosteroids given one hour prior to administration. The patient's performance status at baseline was reported as 2 and had been deteriorating, with wheelchair use noted before administration. About 4 to 5 hours after the initial dose, the patient developed pyrexia, which was treated with acetaminophen and dexamethasone, followed by tocilizumab. Despite repeated doses of acetaminophen, steroids, and two administrations of tocilizumab on (b) (6), pyrexia persisted and the patient subsequently developed tachycardia, renal impairment (creatinine increasing from 1.17 mg/dL pre-treatment to 4.5 mg/dL by (b) (6)), hyperkalaemia (serum potassium rising from 4.8 to 7.2 mEq/L), elevated CRP (from baseline 4.26 mg/dL to 23.49 mg/dL), markedly increased interleukin-6 levels (34,000 on (b) (6)), and oliguria despite IV fluid infusion. The infectious work-up included negative blood cultures, while sputum culture was positive for Group G Streptococcus, and chest X-ray did not reveal evidence of pneumonia. Given the inconclusive overall findings of the infectious evaluation, treatment with ceftriaxone was initiated. The clinical course was complicated by worsening liver enzyme elevations, hyperferritinaemia (2230), multiple organ dysfunction, and poor overall condition attributed to tumor burden. On (b) (6), cardiac arrest secondary to hyperkalaemia from renal failure was reported, and death was confirmed without autopsy. The cause of death was variably reported as cytokine release syndrome, infection, renal failure, hyperkalaemia, cardiac arrest, and ultimately small cell lung cancer. Amgen's assessment noted that this case described CRS clinical course complicated by group G streptococcal infection followed by renal failure, hyperkalaemia, cardiac arrest, and multiple organ dysfunction syndrome in the setting of large SCLC tumor burden, diabetes mellitus, and hypertension, with the overlapping impact of infection, poor baseline status, and tumor-related factors limiting definitive causality assessment of the fatal event.
- Case 8: (b) (6) Serious, Spontaneous Report This case involved a 57-year-old patient with EGFR mutation-positive adenocarcinoma that progressed to SCLC stage IV with liver metastases, along with comorbidities including bronchial asthma, breast cancer, diabetes mellitus, and tobacco use. On (b) (6), the patient received tarlatamab 1 mg following dexamethasone premedication. Within minutes of infusion

completion, the patient developed chills, dyspnea, hypoxia, and pyrexia, treated with acetaminophen, chlorpheniramine, dexamethasone, and tocilizumab. Despite initial treatment, the patient progressed to hypotension, tachycardia, and persistent fever requiring noradrenaline support. By (b) (6) acute kidney injury developed with markedly decreased urine output, necessitating ICU transfer and continuous hemodiafiltration. Laboratory findings showed progressive multi-organ dysfunction with hepatic dysfunction, worsening renal parameters, elevated LDH, hyperferritinaemia, elevated CRP, and cytopenia. The patient developed respiratory failure, edema, encephalopathy, and multi-organ dysfunction despite intensive management. Death occurred on (b) (6), attributed to CRS resulting in multiple organ dysfunction syndrome. While CRS was assessed as related to tarlatamab, Amgen's assessment noted that multiple comorbidities and advanced disease may have contributed to the fatal outcome.

- Case 9: (b) (6) Serious, Spontaneous Report This case involved a 73-year-old male with extensive stage IV SCLC with metastases to brain, pleura, liver, and pancreas, plus comorbidities including sarcoidosis, cardiac sarcoidosis, diabetes mellitus, and hypothyroidism. The patient received tarlatamab 1 mg on (b) (6), as third-line treatment with corticosteroid premedication. On (b) (6) he developed fever (38.0-38.9°C) that resolved with dexamethasone. On (b) (6) the patient progressed to hypoxia requiring oxygen support, tocilizumab, and eventually hypotension (BP 60-69 mmHg) treated with noradrenaline and pulse steroids. He experienced transient depressed consciousness that initially improved. Laboratory findings showed inflammation, liver dysfunction, and renal impairment (CRP 40 mg/L, elevated AST/ALT, creatinine 3.5 mg/dL). On (b) (6) consciousness deteriorated again despite full oxygen support, and death occurred at 3:00 P.M. CRS was retrospectively graded as grade 5 per ASTCT criteria. While the Investigator assessed CRS as possibly related to tarlatamab, Amgen's assessment noted that multiple comorbidities, extensive metastatic disease, and management medications may have contributed to the fatal outcome.
- Case 10: (b) (6) This case involved an 83-year-old male patient with SCLC and other current conditions including diabetes mellitus and unspecified heart disorder, with past medical history, prior procedures, and prior anti-cancer therapies (except unspecified cancer chemotherapy) not reported. On (b) (6), the patient received tarlatamab 1 mg with steroid premedication given before dosing and fluid transfusion given after dosing. After 2 days, on (b) (6), the patient developed CRS characterized by tachycardia progressing to cardiac failure, with pyrexia, hypoxia, and hypotension reportedly absent. Management included dexamethasone 8 mg intravenously once every 8 hours (up to 3 doses) and tocilizumab, with transfer to the intensive care unit. On an unspecified date, the patient reported infection, which was considered an alternative factor related to tocilizumab, but no details were provided. On (b) (6), death occurred with the cause of death reported as CRS, and autopsy status was unknown. Tarlatamab was withdrawn for the events of cardiac failure and

infection on an unspecified date. The Investigator assessed CRS and cardiac failure as possibly related to tarlatamab and assessed infection as not related to tarlatamab. Amgen's assessment noted that although CRS and cardiac failure were considered possibly related to tarlatamab, the patient's pre-existing heart disease likely contributed to the overall clinical deterioration leading to cardiac failure and death. Furthermore, the CRS was only characterized by presence of tachycardia, while fever (a hallmark of CRS), hypoxia, and hypotension per ASTCT criteria were not documented, making the diagnosis of CRS inconclusive.

- Case 11: (b) (6) This case described a patient with unknown gender, with indication, current medical condition, past medical history, prior procedures, prior anti-cancer therapies, and concomitant medications not provided. The patient began tarlatamab on an unknown date, and according to the reporting pharmacist, tarlatamab was administered at an initial dose of 1 mg followed by an escalation to 10 mg. Within 3 to 4 days of dosing, the patient's condition deteriorated rapidly, leading to death attributed to CRS, with no details of specific clinical manifestations, treatment, or hospital course provided. It was unknown if an autopsy was performed, and action taken with tarlatamab was not reported. The outcome of CRS was fatal, and the outcome of general physical health deterioration was unknown, with the Investigator not providing a causality assessment for either event. Amgen's assessment noted that the causality assessment of CRS and cause of death could not be established due to missing information including dates of tarlatamab administration, onset date of CRS, clinical course, diagnostic criteria, and treatment of the event, which are crucial for establishing a timeline and understanding the sequence of events that may have led to CRS occurrence. Additionally, the case lacked details regarding the patient's medical history and any concomitant therapy that might have been ongoing at the time of the event, information essential to evaluate any pre-existing conditions or medications that could have contributed to the cause of death.
- Case 12: (b) (6) This case described a 60-year-old male patient with SCLC, with current medical condition, past medical history, prior procedures, prior anti-cancer therapies, and concomitant medications not provided. The patient began Imdelltra on an unknown date, and shortly after Cycle 2 Day 5, the patient developed CRS and went to an outside community hospital that was unfamiliar with bispecific T-cell engager (BiTE) therapy. At the local facility, the patient was treated for presumed sepsis rather than CRS and subsequently died, reportedly due to untreated CRS. No additional clinical details, including symptom onset, laboratory results, or treatment interventions, were available. The outcome of sepsis was unknown, and action taken with tarlatamab and causality assessment for CRS and sepsis were not provided, with autopsy status unknown. Amgen's assessment noted that the causality assessment of CRS and cause of death could not be established due to missing information including dates of tarlatamab administration, onset date of CRS, clinical course, diagnostic criteria, and treatment of the event, which are crucial for establishing a timeline and understanding the sequence of

events that may have led to CRS occurrence. Additionally, the case lacked details regarding the patient's medical history and any concomitant therapy that might have been ongoing at the time of the event, information essential to evaluate any pre-existing conditions or medications that could have contributed to the cause of death.

- Case 13: (b) (6) This case described a 70-year-old female patient with extensive small cell lung cancer and poor clinical condition who received the first dose of tarlatamab on (b) (6). Following treatment initiation, she experienced severe CRS and renal failure as reported by a nurse, and subsequently died on (b) (6), while hospitalized. The cause of death was not definitively established, with the nurse citing multiple contributing factors including severe CRS, renal failure, and the patient's poor baseline condition. No information was provided regarding treatment administered for the adverse events or autopsy findings, and the outcomes of CRS and renal failure were reported as unknown. Amgen's assessment noted that causality could not be established due to missing information including onset date of CRS, clinical course, and treatment details, as well as lack of patient medical history and concomitant therapy information essential for evaluating pre-existing conditions or medications that could have contributed to death.

Expectations on Safety in the Postmarket Setting

Data:

Not applicable

The Applicant's Position:

The safety profile of tarlatamab is adequately characterized in the current submission, with toxicities appropriately represented in the cumulative safety database and reflected in the existing U.S. Prescribing Information. Routine pharmacovigilance activities will continue to monitor and further characterize the safety profile of tarlatamab. The ongoing and planned clinical studies will contribute additional safety information to further elucidate the safety profile of tarlatamab.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. The safety database for patients treated with tarlatamab is relatively small (n=473). (b) (4) Given this, the safety of tarlatamab should continue to be monitored in the postmarketing setting including for CRS.

8.2.11. **Integrated Assessment of Safety**

Data:

The key risks with tarlatamab treatment are as follows:

Cytokine release syndrome (CRS)

- Across the studies, CRS events were reported in 57% of subjects who received the 10 mg dose of tarlatamab. Most of the CRS events were low grade in nature , rarely escalating to require hospital-required interventions. No fatal events have been reported. Events of CRS occur almost exclusively after the first 2 infusions of tarlatamab with few grade 2 and higher events reported from cycle 1 day 15 and beyond. In general, CRS is manageable and reversible when appropriate prevention, monitoring, and interventions are implemented as outlined in the Dosage and Administration section of the product labeling. Management strategies include step dosing, use of concomitant medications (eg, pre-infusion dexamethasone and postinfusion IV fluids), and treatment of CRS-related symptoms with oral antipyretics, corticosteroids, oxygen supplementation, IV fluids, vasopressors, and/or anti-interleukin6 therapy. In rare instances, tarlatamab treatment interruption or discontinuation may be required.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

- Across the studies, ICANS and associated neurological events have been reported in 11% of subjects who received the 10 mg dose of tarlatamab. Most of the events were mild or moderate with less than 1% grade 3 or above and rarely required treatment discontinuation or dose interruption. A single reported fatal event of ICANS was deemed by Amgen to be confounded by multiple factors. The risks can be adequately mitigated by monitoring patients for signs and symptoms of ICANS following tarlatamab infusion, administration of corticosteroids for management of symptoms, and temporary interruption or discontinuation depending on the severity of the event.

Tarlatamab was generally well tolerated, with a low rate of adverse events leading to treatment discontinuation across the studies in the integrated analysis (6.1% in the 10 mg dose group).

In Study 20210004, the overall incidence of adverse events was similar between tarlatamab and SOC chemotherapy arms, but the incidence of grade ≥ 3 adverse events grade ≥ 4 adverse events, and adverse events leading to dose interruptions and dose discontinuations were lower in the tarlatamab group compared with the SOC chemotherapy group.

Routine risk minimization activities (ie, risk communications and management guidance through prescribing information or product packaging) are considered adequate to address the prevention, monitoring, and treatment of safety concerns associated with the use of tarlatamab.

The Applicant's Position:

Tarlatamab is generally well tolerated. The key safety concerns for tarlatamab are CRS and neurologic toxicity, including ICANS. The safety risks associated with tarlatamab use can be adequately conveyed through clear communication in product labeling (including the current boxed warning to communicate the risks of CRS and neurologic toxicity, including ICANS) and managed through guidance on the Dosage and Administration section in the product labeling, which addresses the prevention, monitoring, and treatment of safety concerns associated with tarlatamab use. Other significant adverse events (infections, hepatotoxicity, and hypersensitivity) are included in the Warnings and Precautions section of the label. Therefore, routine pharmacovigilance activities and routine risk minimization activities are considered adequate. The safety profile was acceptable and manageable in adult subjects with SCLC with disease progression on or after platinum-based chemotherapy.

The FDA's Assessment:

In general, FDA agrees that the safety profile appears manageable and acceptable in the context of a life-threatening disease given the demonstrated efficacy of tarlatamab.

Overall safety outcomes in terms of Grade ≥3 TEAEs and TEAEs that led to treatment interruption or discontinuation were lower in the tarlatamab arm compared with the SOC arm, while the incidence of Grade 5 TEAEs and serious TEAEs were similar between arms. In general, the safety profile was consistent with that described for tarlatamab in the current product labeling. However, there was one fatal event of ICANS in DeLLphi-304 and there were several fatal events of CRS reported in the postmarketing setting. Given this, the boxed warning in the labeling will be updated to indicate the potential for fatal events. The most common AEs (≥20%) observed with tarlatamab were CRS (56%), fatigue (39%), decreased appetite (37%), constipation (30%) pyrexia (29%), dysgeusia (28%), musculoskeletal pain (27%), and nausea (25% each). Serious adverse reactions occurring in >3% of patients who received tarlatamab included CRS (17%), pyrexia (6%), pneumonia (5%) and immune effector cell-associated neurotoxicity syndrome (ICANS; 3.6%). Fatal adverse in patients who received tarlatamab included one fatal adverse reaction of ICANS (0.4%); fatal adverse reactions occurring in more than one patient included pneumonia (1.6%), cardio-respiratory arrest (1.6%), and sepsis (0.8%).

(b) (4)

From review of patient subgroups defined by selected intrinsic and extrinsic factors, no new safety/toxicity trends were observed.

The key safety concerns for tarlatamab include cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), both of which are included in a boxed warning in the U.S. Prescribing Information (USPI). Other safety concerns warranting inclusion in the Warnings and Precautions section of the USPI include hepatotoxicity, infections, cytopenias, and hypersensitivity. There were no safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of tarlatamab.

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SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

DeLLphi-304 (Study 20210004) is a multicenter, international, open-label, randomized trial that enrolled patients with SCLC whose disease has progressed after one prior platinum-containing regimen. Patients were randomized 1:1 to receive tarlatamab or investigator's choice of SOC therapy (lurbinectedin, amrubicin, or topotecan).

Overall survival (OS) was the primary endpoint and achieved statistical significance at the first interim analysis with a 5.3 month median survival advantage over SOC. The hazard ratio for OS was 0.60 (95% CI: 0.47, 0.77; $p < 0.001$), which translated into a median OS of 13.6 months (95% CI: 11.1, NE) in the tarlatamab arm and 8.3 months (95% CI: 7, 10.2) in the SOC arm. At the original DCO of January 29, 2025, the median survival follow up was less than the median OS estimate of the tarlatamb arm, which was estimated around the timing of the last observed event. To obtain a more robust median OS estimate, FDA requested an updated OS analysis with the 90-day safety update DCO (4/29/2025). With an additional 3 months of follow-up at 87% IF, the HR estimate was 0.58 (95% CI: 0.46, 0.73) and median OS estimates were consistent with those at the OS IA: 13.6 months (95% CI: 11.9, NE) for tarlatamab and 8.4 months (95% CI: 7.2, 10.2) for SOC.

The key secondary endpoint for this trial, progression-free survival (PFS) by investigator, was tested hierarchically after OS and was also statistically significant. Tarlatamab demonstrated a 1 month benefit over SOC with hazard ratio of 0.72 (95% CI: 0.59, 0.88), $p < 0.001$, with a median PFS of 4.2 months (95% CI: 3.0, 4.4) for patients receiving tarlatamab and 3.2 months (95% CI: 2.9, 4.2) for patients receiving SOC. During the review, FDA investigated the RECIST tumor assessments of 12 patients with non-target lesion progression and noted that 24 patients (21 on SOC and 3 on tarlatamab) were censored early due to new anti-cancer therapy without evidence of radiographical progression. These issues did not materially impact the statistically significant result.

Five PRO-based endpoints derived from EORTC QLQ-C30 and EORTC QLQ-LC13 were to be tested hierarchically in two groups sequentially if PFS achieved statistical significance. The first level of PRO-based endpoints included dyspnea, chest pain, cough, and were to be tested using Holm's procedure. If all three were statistically significant, testing was to continue with physical functioning and global health status. While dyspnea and cough reached statistical significance, chest pain failed to reach statistical significance halting all further testing of PRO-based endpoints.

Acknowledging statistical significance of the PRO-based endpoints of dyspnea and cough, due to limited clinical meaningfulness, (b) (4).

After 18 weeks, 149 patients (59%) receiving tarlatamab and 116 (45%) patients randomized to SOC were still on treatment. Although the compliance rate is acceptable at 79% and 76% respectively, the available data rate was only 46% and 35%, which reflects the overall level of data missingness. Acknowledging that this protocol was developed before the current PRO technical specification guidance in oncology recommending continued collection of PRO assessments after treatment discontinuation when assessing comparative benefit, this analysis only included PRO measurements collected while patients were still on treatment. This presents a statistical concern as comparisons are being performed between treatment arms only using available data and therefore results of PRO-based endpoints are subject to bias due to the amount and reasons for missing data.

The primary analysis method, MMRM, assumes that patients who missed PRO assessment would benefit the same way as those who were still on treatment and completed PRO assessment. This assumption is not realistic, particularly for those experiencing an AE, whose disease progressed, or who have died, which accounts for roughly 52% of the patient population. Ultimately, the PRO-based dyspnea endpoint was statistically significant and statistical significance was shown to be robust based on a variety of sensitivity analyses, including tipping point analyses, conducted by both the Applicant and FDA. However, the magnitude of the treatment effect remains uncertain as the treatment effect estimates vary greatly under different missing data assumptions. Given the above considerations, a statement of statistical significance and a descriptive visual of mean change from baseline in dyspnea score at week 18 for the patients who reported PRO at both baseline and week 18 were included in labeling,

With a statistically significant and clinically meaningful 5.3 months median OS advantage over SOC, tarlatamab has demonstrated substantial evidence of effectiveness for the treatment of adult patients with ES-SCLC with disease progression on or after platinum-based chemotherapy.

8.4. **Conclusions and Recommendations**

The FDA's Assessment:

The primary study supporting this application, DeLLphi-304 (Study 20210004), is a multicenter, international, open-label, randomized trial that enrolled patients with SCLC whose disease has progressed after one prior platinum-containing therapy regimen. A total of 509 patients were randomized 1:1 to receive tarlatamab or investigator's choice of standard of care (SOC) therapy. Patients received treatment until disease progression, unacceptable toxicity or another criteria for discontinuation was met. The primary endpoint of DeLLphi-304 was overall survival (OS) and key secondary endpoints for the trial were progression free survival (PFS) as assessed by investigator according to RECIST v1.1 along with patient reported outcomes (dyspnea, chest pain, cough, physical functioning and global health status) for the comparison of the tarlatamab arm with the standard of care arm.

At the first prespecified interim analysis of OS, with a data cutoff date of January 29, 2025, when approximately 76% of the expected OS events have occurred, results for both OS and PFS were statistically significant. The hazard ratio (HR) for OS was 0.60 (95% CI: 0.47, 0.77; p <0.001) favoring the tarlatamab arm with a median OS of 13.6 months (95% CI: 11.1, NE) in the tarlatamab arm and 8.3 months (95% CI: 7, 10.2) in the SOC arm. In a pre-specified exploratory subgroup analysis, the HR for OS was similar between patients with a chemotherapy-free interval (CFI) <90 days (n=223) and patients with a CFI ≥90 days (n=286), with HRs of 0.60 (95% CI: 0.43, 0.84) and 0.65 (95% CI: 0.45, 0.93), respectively. The HR for PFS was 0.72 (95% CI: 0.59, 0.88; p= <0.001) with a median PFS of 4.2 months (95% CI: 3, 4.4) in the tarlatamab arm and 3.2 months (95% CI: 2.9, 4.2) in the SOC arm. ORR was 35% (95% CI: 29, 41) in the tarlatamab arm versus 20% (95% CI: 16, 26) in the SOC arm. In addition, the PRO endpoint of mean change from baseline in dyspnea as assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 at week 18 demonstrated a statistically significant improvement in patients randomized to tarlatamab compared to SOC.

The effect on OS was generally consistent across subgroups presented by the Applicant with the exception of the subgroup of patients who were from North America and patients whose tumors had DLL3 expression <25%. The subgroup of patients from North America had a a total of 28 patients (13 in the tarlatamab arm and 15 in the SOC arm) and showed an OS HR of 1.5 (95% CI: 0.55, 4.18). Ad hoc analysis suggested that the patients who received tarlatamab in this subgroup had a higher median age, a lower proportion of patients with ECOG PS, as well as a higher proportion of patients with liver metastases and a higher median sum of diameters than patients who received SOC. In addition, 7 patients who received SOC received subsequent tarlatamab. Given this, FDA attributes the subgroup results to small patient numbers, imbalances in demographics and disease characteristics and receipt of tarlatamab as subsequent therapy in patients who received SOC. In addition, the OS HR results in other regions, including Europe, provide support for the applicability of the OS results in the ITT population to the U.S. population of patients with ES-SCLC. The OS HR for patients whose tumors had a DLL3 expression <25% was 0.95. However, the OS HR for patients with no DLL3 expression at moderate or strong intensity staining was 0.75 (95% CI: 0.32, 1.78). Therefore, for OS, there does not appear to be a direct correlation with DLL3 expression. However, given the mechanism of action of tarlatamab, it will be important to review these subgroup data in future potential marketing applications for tarlatamab.

Overall safety outcomes in terms of Grade ≥3 TEAEs and TEAEs that led to treatment interruption or discontinuation were lower in the tarlatamab arm compared with SOC, while the incidence of Grade 5 TEAEs and serious TEAEs were similar between both arms. In general, the safety profile was consistent with that described for tarlatamab in the current product labeling. However, there was one fatal event of ICANS from DeLLphi-304 and there were several fatal events of CRS in the postmarketing setting. Given this, the boxed warning in the labeling will be updated to indicate the potential for fatal events.

(b) (4)

(b) (4)

The key safety concerns for tarlatamab include cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), both of which are included in a boxed warning in the U.S. Prescribing Information (USPI). Other safety concerns warranting inclusion in the Warnings and Precautions section of the USPI include hepatotoxicity, infections, cytopenias, and hypersensitivity. There were no safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of tarlatamab. With the information included in product labeling, the safety profile appears manageable and is acceptable in the context of a life-threatening disease given the demonstrated efficacy of tarlatamab

The results from the DeLLphi-304 trial meet the statutory evidentiary standard for traditional approval and provide substantial evidence of effectiveness of tarlatamab for the treatment of patients with ES-SCLC with disease progression on or after platinum-based chemotherapy. The observed statistically significant improvement in OS with a HR of 0.60, corresponding to a 5.3-month difference in median OS, is clinically meaningful and represents a major improvement for patients with ES-SCLC. The positive OS results are supported by a statistically significant benefit in PFS, as well as a higher ORR in the tarlatamab arm vs the SOC arm. In addition, the PRO endpoint of mean change from baseline in dyspnea as assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 at week 18 demonstrated a statistically significant improvement in patients randomized to tarlatamab compared to SOC. The available data supports a conclusion that the clinical benefits of tarlatamab therapy in this patient population outweigh its risks.

Based on an overall favorable risk-benefit assessment, the results of the DeLLphi-304 study support a recommendation of traditional approval for tarlatamab for the following indication:

Tarlatamab (IMDELLTRA) for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

8.4.1. Approach to Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication *(enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response)*:

   Tarlatamab (IMDELLTRA) for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*
   a. Adequate and well-controlled clinical investigation(s):
      i. ☒ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR
   b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

      OR
   c. ☐ Evidence that supported SEE from a prior approval *(e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)*[2]

3. Complete response, if applicable
   a. ☐ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)
[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)
[3] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

X	X
Primary Statistical Reviewer	Statistical Team Leader

Version date: March 1, 2024 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

X	X
Primary Clinical Reviewer	Clinical Team Leader

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not refer this supplemental application to an advisory committee or seek input from other external consultants as no significant efficacy or safety issues were identified during the review that required external input and the application did not raise significant public health questions regarding the role of tarlatamab for the proposed indication.

10 Pediatrics

The Applicant's Position:

Tarlatamab was not studied in pediatric subjects. Given that the molecular target of tarlatamab, delta-like ligand 3 (DLL-3), was moved to the nonrelevant molecular target list leading to waiver, FDA Reauthorization Act of 2017 requirements no longer apply, and given tarlatamab's orphan drug designation, Amgen is exempt from the requirements of the Pediatric Research Equity Act.

The FDA's Assessment:

FDA agrees with the Applicant's position.

11 Labeling Recommendations

Data:

This is a supplemental application, please see annotated label in Module 1 for proposed labeling.

Table 31. Summary of Significant Labeling Changes (High level changes and not direct quotations)

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
BOXED WARNING		FDA revised the text to include fatal reactions for both cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS).
2 DOSAGE AND ADMINISTRATION 2.1 Important Dosage and Administration Information		FDA included "and Administration Information" to the subheading and provided a more specific laboratory monitoring schedule.
2.2 Recommended Dosage and Administration		FDA retained the approved recommended dose and schedule, and provided minor editorial revisions for clarity.
2.3 Recommended Concomitant Medications for IMDELLTRA Administration for Cycle 1 Day 1 and Cycle 1 Day 8 2.4 Restarting IMDELLTRA After Dosage Delay 2.5 IMDELLTRA Dosage Modifications and Adverse Reaction Management 2.6 Preparation		FDA retained the approved text and provided minor editorial revisions for clarity.
5 WARNINGS AND PRECAUTIONS		FDA revised this subsection to reflect the new safety population, N=473.

5.1 Cytokine Release Syndrome		
5.2 Neurologic Toxicity Including ICANS		FDA revised this subsection to present the specific adverse reaction terms observed in patients who experienced ICANS.
5.3 Cytopenias		FDA specified that the incidences presented in this subsection are based on laboratory abnormalities.
5.4 Infections 5.5 Hepatotoxicity 5.6 Hypersensitivity		FDA revised these subsections to reflect the new safety population, N=473.
6 ADVERSE REACTIONS 6.1 Clinical Trials Experience		FDA revised the description of the pooled safety population to reflect the total number of patients who received IMDELLTRA at the recommended dose and schedule, N-473.
		The safety of DeLLphi-304 was added. All numbers were adjudicated by FDA. Text from the previous approval describing DeLLphi-300 and DeLLphi-301 was retained.
8.5 Geriatric Use		Text was revised to reflect the safety population, N-473
12 CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics		FDA provided minor revisions for clarity.
12.6 Immunogenicity		Immunogenicity subsection was revised to reflect the maximum 3 year treatment period.
14 CLINICAL STUDIES 14.1 Small Cell Lung Cancer		The efficacy of DeLLphi-304 was added. FDA provided editorial revisions for clarity and brevity. All numbers were adjudicated by FDA. Patient Reported Outcomes were

		limited to those that were statistically significant and the figure was revised for clarity.
17 PATIENT COUNSELING INFORMATION		Minor editorial revisions for clarity.
MEDICATION GUIDE		FDA provided editorially revisions for consistency with the USPI. Please see reviews by Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP).

The Applicant's Position:

The draft USPI is provided with this marketing application.

The FDA's Assessment: The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

There were no significant safety concerns identified during the review of this supplement requiring risk management beyond labeling or warranting consideration for a risk evaluation and mitigation strategy (REMS) to ensure the safe and effective use of tarlatamab for the indicated population. Recommendations for the safe and effective use of tarlatamab are provided in the US prescribing information as well as in the patient medication guide.

13 Postmarketing Requrements and Commitment

The FDA's Assessment:

No new postmarketing requirements or commitments are needed at this time.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes _X_ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	_X_ Yes __ No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _X_ No

A PMC (PMC 4635-3) was issued at the time of the initial approval of tarlatamab for an integrated analysis from ongoing, completed, or planned clinical trials and other potential data sources as appropriate enrolling a sufficient representation of U.S. racial and ethnic minority patients that is reflective of the U.S. population of patients with SCLC, to further characterize the efficacy, safety and pharmacokinetics of tarlatamab in these patients, and this PMC remains open.

On June 18, 2025, FDA received the final report for the following post-marketing requirement listed in the May 16, 2024, post-approval post-marketing requirement letter:

PMR 4635-1: Conduct a multicenter randomized clinical trial intended to verify and describe the clinical benefit of tarlatamab in patients with extensive stage small cell lung cancer (ES-SCLC) who have had disease progression on or after platinum-based chemotherapy.

PMR 4635-2: Conduct an integrated safety analysis of data from patients with extensive stage small cell lung cancer to further characterize the long-term incidence, severity, and outcome of the known serious risks of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and neurologic toxicity. Include a comprehensive analysis from all available data sources including but not limited to patient-level and pooled analyses of ongoing and completed clinical trials. These data could also be obtained from the confirmatory trial titled

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

FDA reviewed the submission and determined that the above PMRs were fulfilled. The results of Study DeLLphi-304 verify the clinical benefit of tarlatamab for the indication under accelerated approval, treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy, fulfilling PMR 4635-1. Additionally, safety data from Study DeLLphi-304 and integrated safety analyses based on the pooled data provided adequate data to further characterize the long-term incidence, severity, and outcome of the known serious risks of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and neurologic toxicity in patients who received tarlatamab, fulfilling PMR 4635-2.

14 Division Director (DHOT) (NME ONLY)

X

APPEARS THIS WAY ON ORIGINAL

15 Division Director (OCP)

X _____

APPEARS THIS WAY ON ORIGINAL

16 Division Director (OB)

X _____

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1. References

The Applicant's References:

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19.2. Financial Disclosure

The Applicant's Position:

The Application provided financial disclosure in Form 3455 for all clinical investigators involved in Study 20210004. No concerns were raised regarding the overall integrity of the data.

Covered Clinical Study (Name and/or Number):* 20210004

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2057		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 (none)		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): one investigator with disclosable interest according to CFR 54.2 (f) one investigator with disclosable interest according to CFR 54.2 (b) Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 (PI received funding of 603,391 USD for an investigator initiated (b) (6) when they were with a previous institution and they are a PI on that) Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: 1 (PI holds 1900 Amgen shares) Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		

Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

FDA reviewed the financial disclosures for all study investigators. Of the 2057 investigators participating in DeLLphi-304, 2041 investigators (99%) did not have significant financial disclosures to report.

Fourteen investigators did not provide financial disclosure information but all 14 left the site before the site activation date. There were 2 investigators (0.1%) reported significant financial disclosures. Regarding the 2 investigators who reported significant financial disclosures, one indicated disclosable interest according to 21 CFR 54.2(f) (significant payments of other sorts means payments made by the Applicant of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following the completion of the study) and the other indicated disclosable interest according to 21 CFR 54.2(b) (Significant equity interest in the sponsor of a covered study means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $50,000 during the time the clinical investigator is carrying out the study and for 1 year following completion of the study). The investigator with the 21 CFR 54.2(b) disclosure (b) (4) while the investigator with the 21 CFR 54.2(f) disclosure was a (b) (4) enrolled into DeLLphi-304 from the site. Based on the above, it is the opinion of the FDA clinical review team that the submitted financial disclosures from DeLLphi-304 are very unlikely to have impacted the study in a meaningful way.

19.3. Nonclinical Pharmacology/Toxicology

Data:

All data presented in Section 5, Nonclinical Pharmacology/Toxicology.

The Applicant's Position:

Not Applicable.

The FDA's Assessment:

Not applicable. No new nonclinical pharmacology/toxicology data are provided in the current sBLA.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

The FDA's Assessment:
The PK samples in study 20210004 were analyzed using two methods adapted from the validated method MET-406436. One is the previously cross-validated Electrochemiluminescence (ECL) method BAL-II/MOA/115 in BLA 761344 Seq.0007 in a validation report entitled "Study 154752 Method Validation for Quantification of AMG 757 in Human Serum by ECL Assay". This method was reviewed during review of the orinigal BLA 761344 and method performance in Study 20210004 is reviewed in Table 21. Another ECL method ICSH 20-079 (b) (4) is used for samples in China and validated in BLA 761344 Seq.0093 in a validation report entitled "Study 151089 Validation of a Method for the Determination of AMG 757 in Human Serum Using ECL" and Addendum 01. Method ICSH 20-079 is reviewed in Table 22 below.

Table 32. Performance of method BAL-II/MOA/115 by (b) (4) in Study 20210004 for measurement of tarlatamab (AMG 757) (Amgen Study Number: 157047, Trial Facility Study No.: U-23151)

Parameters	Method Performance Summary	Acceptability
Assay passing rate	48 out of 50 sample analytical runs (96%) met the method acceptance criteria	Yes
Standard curve performance	• Inter-run bias range: -2 to 2% (anchor points excluded) • Inter-run precision: ≤ 4% CV	Yes
QC performance	QC concentrations: 1, 10, 67.5 ng/mL • Inter-run bias range: −8% to 4% • Inter-run precision: ≤ 7% CV • TE ≤ 15%	Yes
Method reproducibility	Incurred Sample Reanalysis (ISR) is ongoing and will be reported in the final report.	NA

	Note: ISR of this method for another study 20200491 was performed at (b) (4) in 211 out of 5049 samples (4.1%) and 195 (92.4%) met predefined acceptance criteria.	
Study sample analysis/ stability	Study samples analyzed for AMG 757 in support of study 20210004 were analyzed within 480 days after collection, which is covered by 917 days of long-term stability at nominal −60 to −80ºC (stability study ongoing, BA report of in section 16.1.13.1 of study 20200491 supplemental CSR reported the data).	Yes

Table 33. Summary of cross-validation results of method ICSH 20-079 by (b) (4) and performance in study 20210004 for measurement of tarlatamab (AMG 757) (Validation Report. 151089)

Bioanalytical method review summary	**Method validation was adequate to support Study 20210004**		
Changes in method	• Calibration curve concentrations modified: 180, 90.0, 45.0, 22.5, 11.3, 5.63, 2.81, 1.41, 0.703, 0.352 and 0.176 ng/mL tarlatamab • Watson LIMS used for data evaluation (instead of SoftMax Pro)		
New validated assay range if any	0.352 to 90.0 ng/mL tarlatamab		
Validation Parameters	**Cross-validation performance**		**Acceptability**
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-1.2 to 2.2%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4.9%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-7.2 to 3.4%	Yes
	Inter-batch %CV	≤ 8.0%	Yes
	Percent total error (TE)	≤ 15.2%	Yes
Cross validation	25 QC samples (five sets of five levels of QCs - ULOQ, HQC, MQC, LQC and LLOQ) were tested. The relative percent		Yes

	difference between the reference and the comparator lab was ≤ 19.4%. Cross-laboratory analysis was not available due to logistical constraints associated with the shipment of incurred samples from an ongoing study between (b) (4) .	
Selectivity & matrix effect	A total of 20 individual lots (10 normal human serum; 5 hemolytic and 5 lipemic) of human serum samples were tested unspiked and spiked at the LLOQ (0.352 ng/mL) and ULOQ (90.0 ng/mL) levels. No matrix effect was observed (%Bias -10.8 to -3.0).	Yes
Dilution linearity & hook effect	Five aliquots of 50,000 ng/mL tarlatamab were serially diluted at 6,000, 600, 90, 50, 10, 1.76, 0.352, 0.088 ng/mL. The %bias of all diluted samples at concentrations 90, 50, 10, 1.76, 0.352 ranged from -5 to -3%. CV% ≤15.7%. Linearity is demonstrated within this range. No hook effect was observed.	Yes. The highest serum concentration observed in study 20210004 sample analysis was 9420 ng/mL.
Bench-top/process stability	Stability was demonstrated for 24 hours 30 minutes at RT and at 2-8°C for 71 hours and 05 minutes with CV% ranged from 0.6-3%.	Yes.
Freeze-Thaw stability	Tarlatamab in human serum is stable up to 6 freeze-thaw cycles (-60 to -80°C) with CV% ≤ 5.9%, bias% -7.8 to 10.8. HQC (67.5 ng/mL) and LQC (1.00 ng/mL) were tested.	Yes
Long-term storage	Long-term stability of tarlatamab in human serum is established for up to 32 days at -60 to -80°C with CV% ≤ 2.5%, bias% -11.6 to 6.4. HQC (67.5 ng/mL) and LQC (1.00 ng/mL) were tested. Stability study is still ongoing. Interim long term stability has been established up to 533 days at -10 to -70°C, per 1.11.2 Response to FDA clinpharm IR Received 10 July 2025 and BAMEM02.151089 stability update	Yes

Method Performance in Study 20210004 (Study ongoing, interim bioanalytical report, sponsor reference number 157658) (Data from study 20210004 section 16.1.13.2, Supportive PK info, and (b) (4) study number 8523-513 interim report)

Assay passing rate	90.3% = 28/31 Out of 31 analytical runs, 3 were rejected.	Yes

Standard curve performance	Standard curves' concentrations were 0.176, 0.352, 0.703, 1.41, 2.81, 5.63, 11.3, 22.5, 34, 90, 180 ng/mL of tarlatamab. • Inter-run bias range: −0.5% to 2.9%Bias • Inter-run precision: ≤ 5.0% CV	Yes
QC performance	QC concentrations: 1, 10, 67.5 ng/mL • Inter-run bias range: −7.8% to −2.4% • Inter-run precision: ≤ 9.8% CV • TE ≤ 17.6%	Yes
Method reproducibility	Incurred sample reanalysis is still ongoing as of 9/12/2025 and will be reported in the Final Report. It has been performed in 8.5% of study samples (45 out of 527) and 97.7% (44) of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	The longest storage duration of any PK study sample was 263 days. Long-term stability study of tarlatamab in human serum at -80 +/- 10°C is still ongoing, and established at least up to 533 days.	Yes

The ADA methods supporting Study 20210004 are BAL/II-MOA/116-02 (b) (4) for global samples and ICSH 20-069-V2 (b) (4) for Chinese samples. The method BAL/II-MOA/116-02 was validated to tolerate up to 10 µg/mL tarlatamab at the presence of anti-tarlatamab antibody positive control (ADA PC) concentration of 12 to 10,000 ng/mL (Validation Report 154753). The method ICSH 20-069-V2 was validated to tolerate up to 20 µg/mL tarlatamab at the presence of 50 to 10,000 ng/mL ADA PC (Validation Report 151090). The median tarlatamab concentration in immunogenicity samples is 546 ng/mL (min-max: 0.506-9420 ng/mL), which are all below the tolerance of these two assays. Therefore, these methods were adequate to support Study 20210004.

Immunogenicity samples were collected pre-dose at C1D1, C2D1, C3D1, C4D1, C6D1, C8D1, C10D1, C12D1, C14D1 in Study 20210004. The presence of ADA decrease the C_{trough} at the timepoints listed below by 5% to 83% (Table 23).

Table 34. Tarlatamab trough concentrations in ADA positive and ADA negative samples at multiple timepoints in Study 20210004

	Geometric Mean of C_{trough} (ng/mL)				GMR (90%CI)		
Time Point	ADA Positive	N	ADA Negative	N	Ratio	Lower Limit	Upper Limit
C1D1	0.2	22	0.2	224	95%	79%	115%

C2D1	147	8	425	197	35%	22%	54%
C3D1	117	5	400	52	29%	14%	63%
C4D1	75	9	430	133	18%	11%	28%
C6D1	322	5	411	111	78%	48%	129%
C8D1	182	4	420	89	43%	24%	77%
C10D1	129	2	432	53	30%	17%	53%

Source: FDA analysis using dataset adis.xpt and adpc.xpt

The labeling pooled immunogenicity data from studies 20160323, 20200491, and 20210004 and updated the treatment duration to 3 years. Per Applicant analysis based on ISS 90d adis dataset, the subject with the longest ADA sample period from the 10 mg group among the three studies is subject ID (b) (6) from study 20200491who is an ADA negative subject, with first dose date (b) (6), last dose date (b) (6), first ADA sample collection date (b) (6), and last ADA sample collection date (b) (6). The time between the last dose date and the first dose date is 3.1 years, and the time between the last ADA sample collection date and the first ADA sample collection date is 3.0 years.

The NAb methods supporting Study 20210004 are MET-407730 (Amgen Research GmbH Munich, Germany) for global samples and 24BASM150 (b) (4) China) for Chinese samples. Both are cell-based bioassays. At the presence of 400 ng/mL ADA PC, both methods can only tolerate up to 24.4 ng/mL tarlatamab (Validation Report. 155881-Amendment, 158112), which is lower than tarlatamab concentration in immunogenicity samples. At the presence of 1,000 ng/mL ADA PC, both methods can only tolerate up to 25,000 ng/mL tarlatamab, which is higher than tarlatamab concentration in immunogenicity samples. Limited data from Study 20210004 suggest that the ADA+/NAb- group do not have significant difference in efficacy compared to the ADA+ group (Table 5). Therefore, there is no evidence showing the presence of clinically meaningful false negative NAb results and there is no immediate concern regarding the drug tolerance issue for the NAb assays. In conclusion, these methods were suitable to support Study 20210004.

19.4.2. Population PK Analysis

19.4.2.1. Executive Summary

The FDA's Assessment:

PK of tarlatamab was characterized by a two-compartment model followed by linear elimination. Compared to the original population PK analysis using PK data from Studies 20160323 and 20200491 of 420 SCLC patients, the updated analysis included new PK data from Ph3 Study 20210004 and additional PK data from Study 20160323 and 20200491 of 702 SCLC patients. The population PK model described the observed data reasonably well. Consistent with the previous analysis, no intrinsic or extrinsic factors are likely to have clinically meaningful impact on exposure.

The proposed dosage of tarlatamab 10 mg IV Q2W appears appropriate.

19.4.2.2. PPK Assessment Summary

The Applicant's Position:

Based on cross-study population PK analyses:

- Population mean (%CV) for CL is estimated to be 0.728 L/day (34%). Vss mean (%CV) based on individual parameters is estimated to be 8.53 L (33%) and terminal half-life mean (%CV) is estimated to be 10.6 days (31%)
- Like other biologics, body weight was found to be correlated with tarlatamab CL, with increase in body weight associated with increase in CL. However, at the clinical regimen of 1 mg on day 1 followed by 10 mg on day 8, day 15, and Q2W thereafter, body weight is not expected to have a clinically relevant impact on tarlatamab efficacy as the point estimate for the difference between high or low body weight subjects relative to a median bodyweight subject of 72.6 kg is estimated to be within the default boundary of 80% to 125%.
- Positive ADA binding status was identified as a significant time-varying covariate on tarlatamab CL. Individuals with positive ADA binding status at any time during the study were estimated to have higher CL. Overall, the impact of ADA on exposures was not clinically relevant as displayed by subgroup analyses for efficacy endpoints in ADA positive and ADA negative subjects (Integrated Summary of Immunogenicity [Module 5.3.5.3]).
- Race was found to be correlated with central volume of distribution (Vc); however, race had no relevant impact on exposures.
- Liver function and number of prior lines of therapy were both found to be statistically correlated with tarlatamab CL, however the estimated effects on exposure are not expected to be clinically meaningful.

Tarlatamab PK were not significantly impacted by other factors such as age, sex, ethnicity, serum albumin, baseline disease burden or ECOG status, or renal function.

General Information		
Objectives of PPK Analysis		The objectives of the analysis were to characterize the population pharmacokinetics of tarlatamab in subjects with small cell lung cancer (SCLC), to evaluate the effects of demographic variables (covariates) on pharmacokinetic (PK) parameters, and to assess the impacts of identified covariates on tarlatamab exposures.
Study Included		20160323, 20200491, 20210004
Dose(s) Included		In these studies, tarlatamab was administered with short or extended intravenous infusion, and using no-step, one-step or two-step dosing regimens. Evaluated target doses included 0.003mg, 0.01mg, 0.03mg, 0.1mg, 0.3mg, 1mg, 3mg, 10mg, 30mg, and 100mg Q2W or 200mg Q3W (Table 2 and Table 5 of Amgen Pharmacometrics Report: 160172)
Population Included		Patients with small cell lung cancer
Population Characteristics (Table 4)	General	Age median (range): 64 (20-86) years Weight median (range): 73 (35-149) kg 456 (65%) male 476 (68%) in White 11 (1.6%) in Black 190 (27%) in Asian 25 (3.6%) in Other
	Organ Impairment	Hepatic impairment (NCI-ODWG): 517 (74%) in Normal 184 (26%) in Mild 1 Missing Renal impairment (CKD based on eGFR): 366 (52%) in Normal 263 (37%) in Mild 68 (9.7%) in Moderate 5 Missing
	Pediatrics (if any)	None
No. of Patients, PK Samples, and BLQ		702 subjects 34 of 11805 (0.29%) post-dose BQL samples
	Rich Sampling	<u>Study 20210004:</u>

Sampling Schedule		Sparse samples were drawn (pre/post infusion only) on day 1 and day 15 in cycle 1, then on day 1 in cycles 2 to 4 (starting in cycle 4, predose only), then on day 1 preinfusion only for every other cycle up to cycle 12. For N=18 subjects at study centers in China, intensive PK sampling was performed: on cycle 1 day 1, samples were collected before and at the end of infusion, 6, 24, 48 and 168 hours postdose. During cycle 2, PK samples were collected on day 1 and day 15 before and at the end of infusion, 6, 24, 48, 168, and 336 hours postdose <u>Study 20160323:</u> Intensive PK samples were collected in Parts A, C and D on days 1, 8 and 15 over a 48-hour period after the start of infusion (SOI) in cycles 1 and 2 (ie. pre-infusion, end of infusion, 6, 24, 48 hours post-SOI for days 1, 8 and 15; additional sampling at 168 hours post-SOI on day 15). Sparse PK samples were collected at pre-infusion and at the end of infusion (EOI) in cycles 3 & 4, and only at pre-infusion in cycles 5-12. Sparse PK samples were collected for Parts E, F and G at pre-infusion and at EOI. For Part G, additional intensive PK samples were collected for cycle 2 only at 24, 48, 168 and 336 hours after SOI. <u>Study 20200491:</u> Sparse samples were drawn before infusion and at end of infusion on days 1, 8 and 15 of cycle 1. Starting cycle 2 through cycle 4, samples were collected at pre- and post-infusion on days 1 and 15. From cycle 5 through cycle 12, only pre-infusion samples were collected on day 1 of each cycle.
	In ITT Population	Not applicable.
Covariates Evaluated	Static	Bodyweight, age, sex, race, ethnicity, albumin, chronic kidney disease stage (CKD) score based on eGFR evaluated by Modification of Diet in Renal Disease (MDRD) formula, overall hepatic impairment scores evaluated by National Cancer Institute Organ Dysfunction Working Group criteria, ECOG score, the number of prior

	anticancer therapies, baseline sum of target lesion diameters
Time-varying	Presence of Antidrug antibody

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM 7.5	Yes
Model Structure	Two-compartment disposition pharmacokinetic model with first order elimination	Yes
Model Parameter Estimates	Table 8 of Amgen Report 160172	Yes
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	RSE and IIV values can be found in Table 8. All shrinkage values were <30%. The estimated model parameters fell within the distribution of 1,000 bootstrap replicates. These results confirmed the stability of the model developed and quantified precision of the parameter estimates. Hence, the reference model was appropriately validated and deemed adequate to analyze the combined dataset (Table 8 of Amgen Report 160172).	Yes
BLQ for Parameter Accuracy	4.5% of PK samples that were pre-dose, 0.29% of PK samples that were postdose and 0.5% of PK samples with date-time issues were excluded from the analysis	Yes
GOF, VPC	GOF: Figure 4 of Amgen Report 160172 pcVPC: Figures 12 and 13 of Amgen Report 160172	Yes
Significant Covariates and Clinical Relevance	Forest plot: Figure 1 of Amgen Report 160172	Yes Statistically significant

		covariates do not result in clinically meaningful change in exposure.
Analysis Based on Simulation (optional)	Section 8.2.3.2 of Amgen Report 160172 Section 9.2 of Amgen Report 160172	Simulation showed steady-state achieved after the third dose.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	Distribution Tarlatamab-dlle steady state volume of distribution is (b) (4) L (33%). Metabolism Tarlatamab-dlle is expected to be metabolized into small peptides by catabolic pathways. Elimination Tarlatamab-dlle's mean terminal elimination half-life (CV%) is (b) (4) days (31%) days and the estimated systemic clearance is (b) (4) L/day (34%) in patients with SCLC.	PK parameters in the labeling were updated to include data from Study 20210004.

Amgen Pharmacometrics Report: 160172

Table 4. Summary of Demographics, Clinical Characteristics and Baseline Covariates

Variable	20160323 P1 N = 266	20200491 P2 N = 220	20210004 P3 N = 216	Overall N = 702
Age (year)				
Mean (SD)	62 (8)	63 (9)	63 (9)	63 (9)
Median (Min-Max)	63 (32-80)	64 (34-82)	64 (20-86)	64 (20-86)
Weight (kg)				
Mean (SD)	76 (19)	74 (16)	72 (15)	74 (17)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Median (Min-Max)	74 (35-149)	72 (41-123)	71 (39-127)	73 (35-149)
Sex				
Male (n/N [%])	150 / 266 (56%)	156 / 220 (71%)	150 / 216 (69%)	456 / 702 (65%)
Female (n/N [%])	116 / 266 (44%)	64 / 220 (29%)	66 / 216 (31%)	246 / 702 (35%)
Race				
Caucasian (n/N [%])	211 / 266 (79%)	138 / 220 (63%)	127 / 216 (59%)	476 / 702 (68%)
Black (n/N [%])	9 / 266 (3.4%)	1 / 220 (0.5%)	1 / 216 (0.5%)	11 / 702 (1.6%)
Asian (n/N [%])	26 / 266 (9.8%)	79 / 220 (36%)	85 / 216 (39%)	190 / 702 (27%)
Others (n/N [%])	20 / 266 (7.5%)	2 / 220 (0.9%)	3 / 216 (1.4%)	25 / 702 (3.6%)
Ethnicity				
Not Hispanic or Latino (n/N [%])	259 / 266 (97%)	215 / 220 (98%)	201 / 216 (93%)	675 / 702 (96%)
Hispanic or Latino (n/N [%])	7 / 266 (2.6%)	3 / 220 (1.4%)	14 / 216 (6.5%)	24 / 702 (3.4%)
Missing (n/N [%])	0 / 266 (0%)	2 / 220 (0.9%)	1 / 216 (0.5%)	3 / 702 (0.4%)
NCI-ODWG				
Normal (n/N [%])	198 / 266 (74%)	157 / 220 (71%)	162 / 216 (75%)	517 / 702 (74%)
Mild* (n/N [%])	68 / 266 (26%)	63 / 220 (29%)	53 / 216 (25%)	184 / 702 (26%)
Missing (n/N [%])	0 / 266 (0%)	0 / 220 (0%)	1 / 216 (0.5%)	1 / 702 (0.1%)
CKD				
Normal (n/N [%])	147 / 266 (55%)	118 / 220 (54%)	101 / 216 (47%)	366 / 702 (52%)
Mild (n/N [%])	94 / 266 (35%)	79 / 220 (36%)	90 / 216 (42%)	263 / 702 (37%)
Moderate** (n/N [%])	21 / 266 (7.9%)	22 / 220 (10%)	25 / 216 (12%)	68 / 702 (9.7%)
(Missing)	4 / 266 (1.5%)	1 / 220 (0.5%)	0 / 216 (0%)	5 / 702 (0.7%)
Baseline Albumin (g/L)				
Mean (SD)	40.1 (5.2)	39.1 (5.0)	42.2 (17.9)	40.4 (10.9)
Median (Min-Max)	40.0 (4.4-74.0)	39.0 (25.0-52.0)	41.5 (26.0-296.0)	40.0 (4.4-296.0)
ECOG Score				
Fully active (n/N [%])	98 / 266 (37%)	60 / 220 (27%)	76 / 216 (35%)	234 / 702 (33%)
ECOG=1 or 2 (n/N [%])	168 / 266 (63%)	160 / 220 (73%)	140 / 216 (65%)	468 / 702 (67%)
Num of Prior Cancer Therapies				
1 prior cancer therapy (n/N [%])	65 / 266 (24%)	4 / 220 (1.8%)	211 / 216 (98%)	280 / 702 (40%)
2 prior cancer therapies (n/N [%])	124 / 266 (47%)	134 / 220 (61%)	5 / 216 (2.3%)	263 / 702 (37%)
≥3 prior cancer therapies (n/N [%])	75 / 266 (28%)	82 / 220 (37%)	0 / 216 (0%)	157 / 702 (22%)
Missing (n/N [%])	2 / 266 (0.8%)	0 / 220 (0%)	0 / 216 (0%)	2 / 702 (0.3%)
Baseline sum of target lesion diameters (mm)				
Mean (SD)	92 (68)	104 (63)	80 (52)	92 (63)
Median (Min-Max)	80 (10-758)	91 (10-300)	68 (10-270)	80 (10-758)
Missing (n/N [%])	1	0	0	1
Presence of binding ADA				
Negative (n/N [%])	245 / 266 (92%)	193 / 220 (88%)	182 / 216 (84%)	620 / 702 (88%)
Positive (n/N [%])	21 / 266 (7.9%)	27 / 220 (12%)	34 / 216 (16%)	82 / 702 (12%)

Table 8. Parameter Estimates for Base Model and Final Model

Parameter	**Base Model Estimate (95%CI)**	Final Model Estimate (95%CI)	Bootstrap Estimate (95%CI)
CL (L/day)	0.707 (0.678, 0.736)	0.728 (0.691, 0.765)	0.728 (0.691, 0.766)
V1 (L)	3.29 (3.16, 3.41)	3.23 (3.10, 3.36)	3.23 (3.12, 3.37)
Q (L/day)	1.11 (0.969, 1.25)	1.15 (0.980, 1.33)	1.15 (0.990, 1.34)
V2 (L)	4.76 (4.40, 5.12)	4.96 (4.56, 5.36)	4.96 (4.59, 5.43)
CLADA1 (binding ADA effect on CL)	-	0.144 (-0.0663, 0.355)	0.146 (-0.0325, 0.392)
CLBW1 (Body weight on CL, proportional change per kg)	-	0.00888 (0.00714, 0.0106)	0.00884 (0.00716, 0.0105)
CLNCI1 (Hepatic function effect on CL [mild vs normal])	-	0.142 (0.0686, 0.216)	0.144 (0.0749, 0.226)
CLNHX1 (Number of Prior Anti-cancer treatment effect on CL [2 vs 1])	-	-0.104 (-0.155, -0.0533)	-0.103 (-0.150, -0.0529)
CLNHX2 (Number of Prior Anti-cancer treatment effect on CL [3+ vs. 1])	-	-0.152 (-0.206, -0.0984)	-0.153 (-0.203, -0.0932)
V1BW1 (Body weight on V1, proportional change per kg)	-	0.00772 (0.00539, 0.0101)	0.00759 (0.00546, 0.00971)
V1RACECD1 (Asian race on V1)	-	-0.0478 (-0.106, 0.0105)	-0.0488 (-0.109, 0.0242)
IIV VAR:CL (OMEGA.1.1.)	0.192 (0.129, 0.255)	0.117 (0.0953, 0.138)	0.116 (0.0968, 0.137)
IIV VAR:V1 (OMEGA.2.2.)	0.162 (0.128, 0.197)	0.142 (0.104, 0.180)	0.141 (0.108, 0.185)
COV:CL-V1 (OMEGA.2.1.)	0.140 (0.0893, 0.192)	0.0927 (0.0707, 0.115)	0.0924 (0.0723, 0.116)
IIV VAR:V2 (OMEGA.3.3.)	-	0.216 (0.0732, 0.358)	0.212 (0.0837, 0.341)
IIV VAR:CLADA (OMEGA.4.4.)	-	0.637 (0.120, 1.15)	0.619 (0.169, 1.21)
RES VAR:EXP	0.218 (0.121, 0.314)	0.204 (0.121, 0.287)	0.202 (0.149, 0.299)

Figure 4. Goodness-of-fit Plots Based on the Final Model

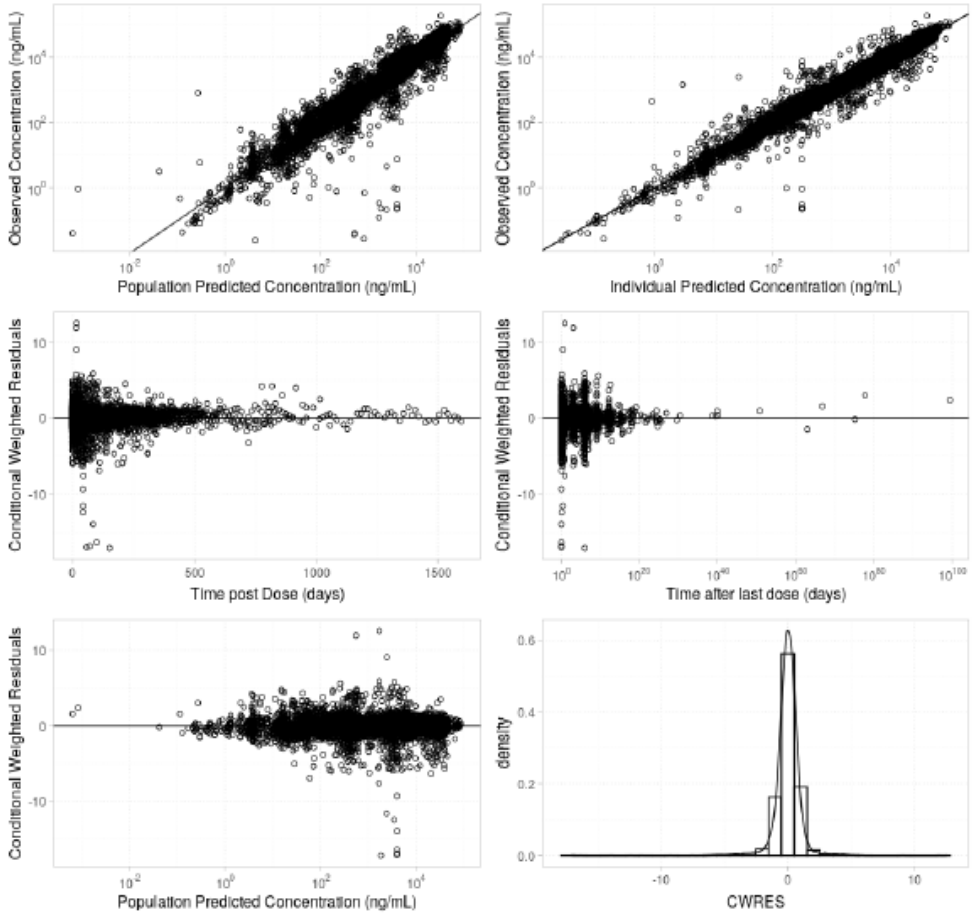


Figure 7. Sex Effect on CL and V1

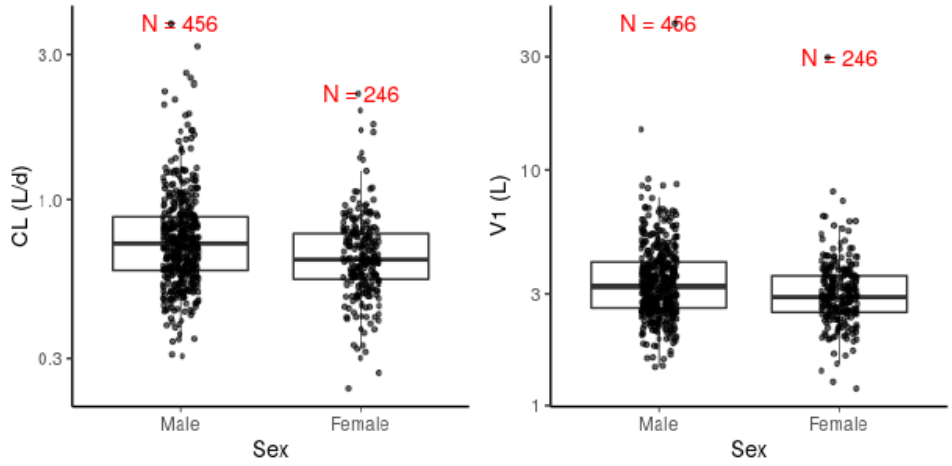


Figure 8. Race Effect on CL and V1

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

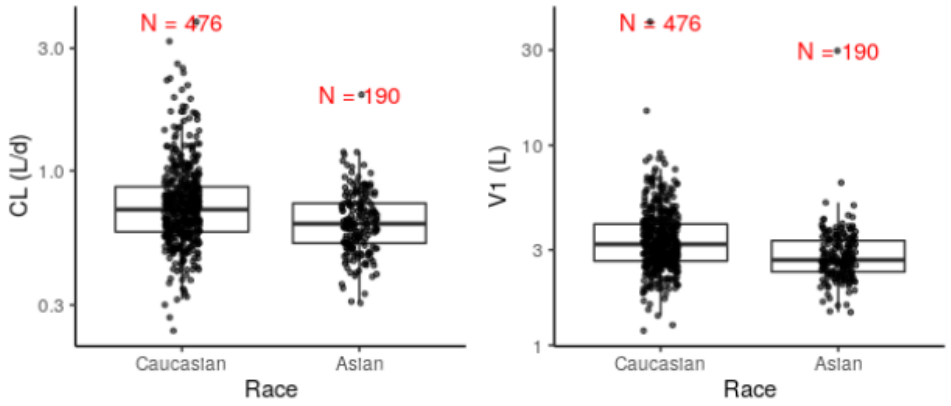


Figure 9. Effect of Kidney and Liver Function on CL

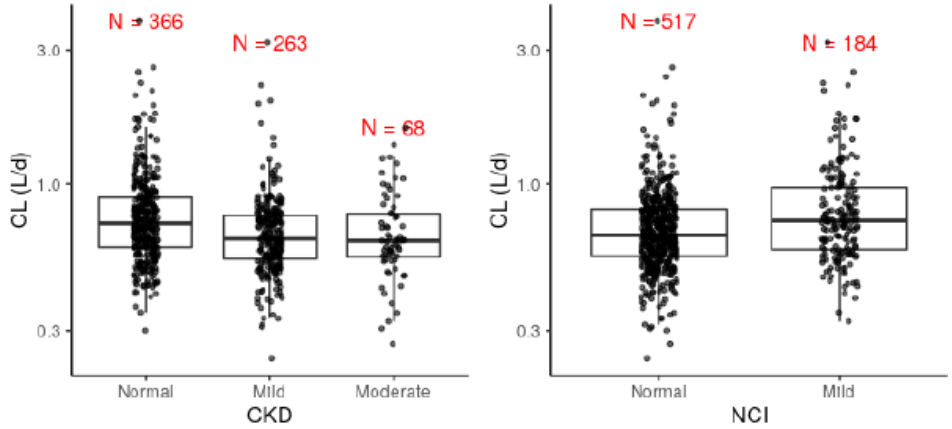


Figure 11. ADA Effect on CL

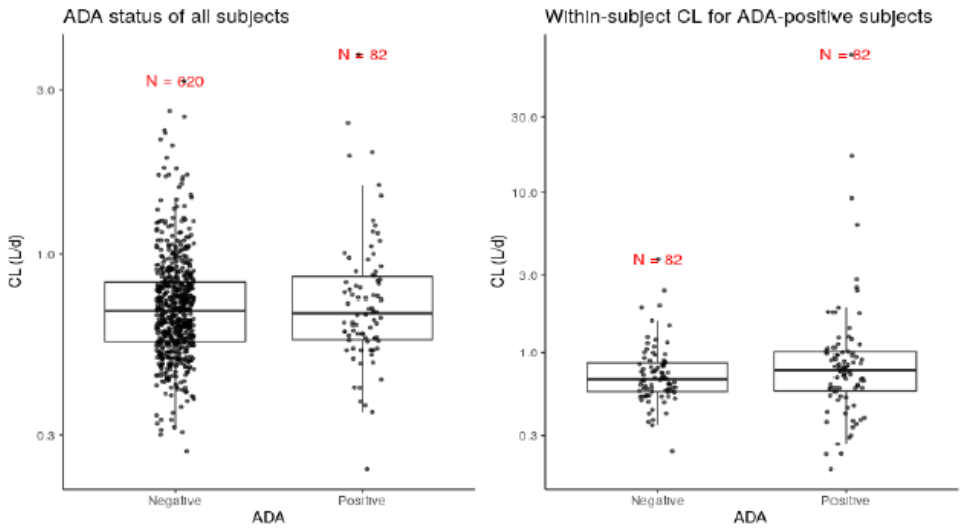
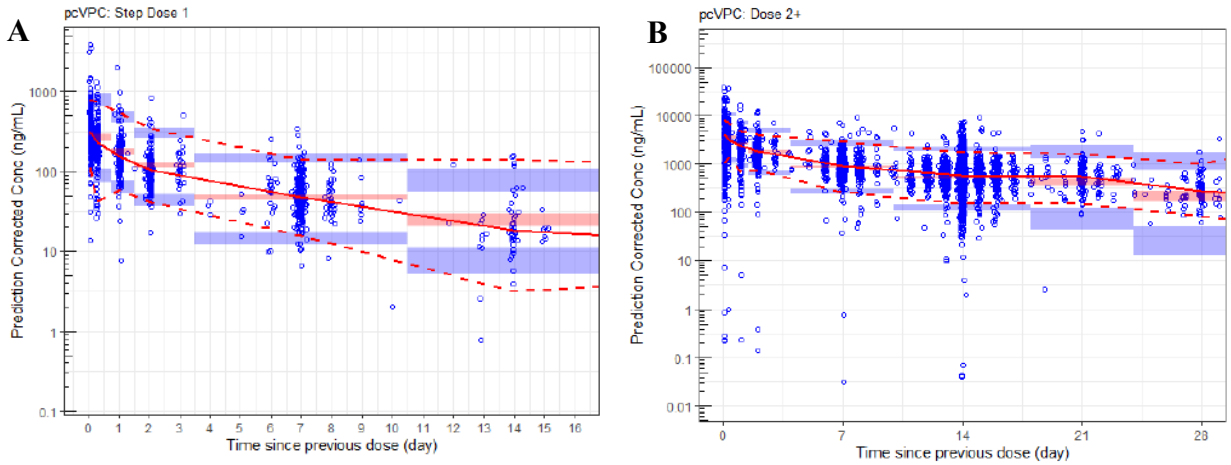
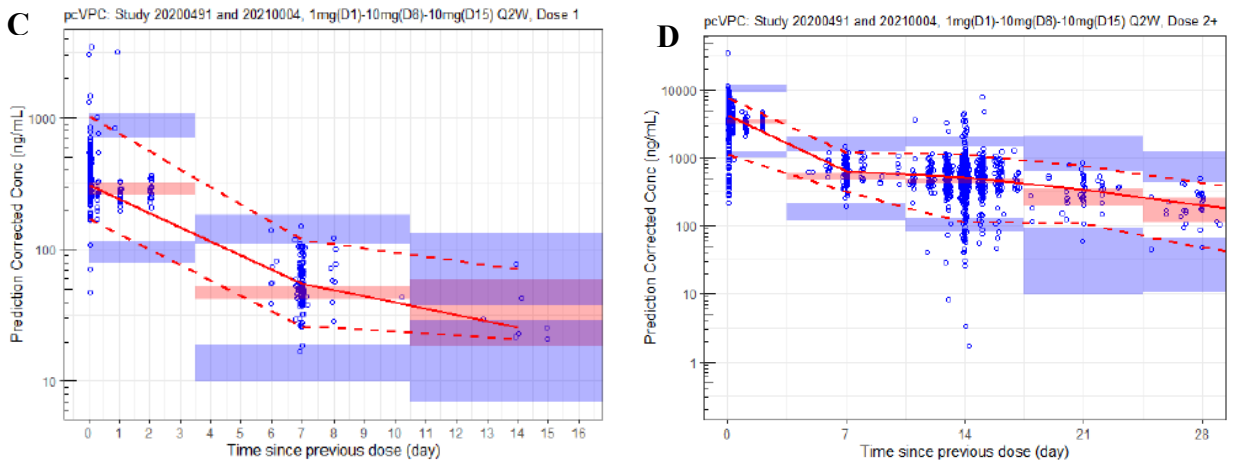


Figure 12-13. Prediction Corrected Visual Predictive Check Stratified by Target Dose





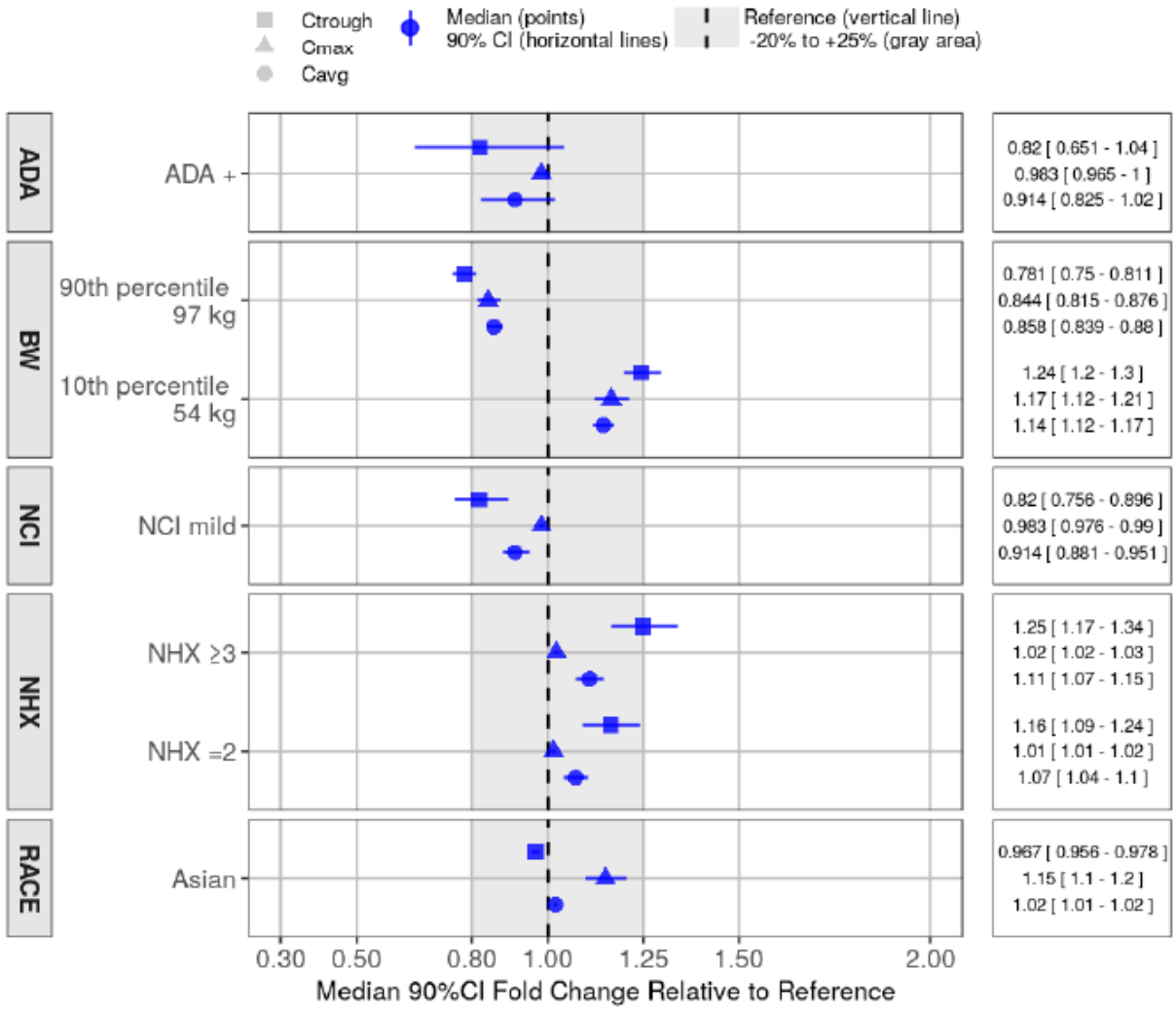
A: Study 20160323, 20200491, 20210004, Dose 1: Step up dose

B: Study 20160323, 20200491, 20210004, Dose 2 and onwards

C: Study 20200491, 20210004, Dose 1: Step up dose

D: Study 20200491, 20210004, Dose 2 and onwards

Figure 14. Forest Plot of Covariate Effects on Tarlatamab Exposures Following 1 mg D1, 10 mg on D8, D15 and Q2W Thereafter Dosing of Tarlatamab



The FDA's Assessment:
The population PK analysis is considered adequate. The intrinsic factors evaluated are not expected to result in clinically meaningful change in exposure.

19.4.2.3. PPK Review Issues

None.

19.4.2.4. Reviewer's Independent Analysis

None.

19.4.3. Exposure-Response Analysis

19.4.3.1. ER (efficacy) Executive Summary

The FDA's Assessment:

Lack of exposure-efficacy (i.e., OS, PFS, ORR, DOR, BTSR) was observed across exposures at the target dosage of 10 mg Q2W, indicating that efficacy is near plateau. Sum of target lesion diameters at baseline and mild hepatic impairment were found to be significantly associated with higher hazard for OS, which are exposure independent and do not warrant a dosage adjustment for exposure difference of <20% in these subgroups.

19.4.3.2. ER (efficacy) Assessment Summary

The Applicant's Position:

Using pooled data across Studies 20160323, 20200491, and 20210004, the relationship between model-estimated averaged concentration over the first cycle and key efficacy endpoints were explored. These analyses confirmed that the exposures associated with the proposed dosing regimen of 10 mg Q2W maximizes the efficacy of tarlatamab.

General Information	
Goal of ER analysis	Characterize the relationships between tarlatamab serum exposures and key efficacy endpoints, including objective response rate (ORR) (complete response [CR] and partial response [PR]), disease control rate (DCR, comprising CR, PR or stable disease [SD]), progression-free survival (PFS), overall survival (OS), duration of response (DOR), and best tumor size response (BTSR, based on percentage change in sum of target lesion diameters from baseline)
Study Included	The dataset for ER analyses consisted of 692 subjects with small cell lung cancer (SCLC) receiving at least one dose of tarlatamab in the monotherapy setting in the phase 1 Study 20160323, phase 2 Study 20200491, and phase 3 Study 20210004
Endpoint	*Primary: OS*

		Secondary: DCR, PFS, ORR, DOR, BTSR	
No. of Patients (total, and with individual PK)		692	
Population Characteristics (Table 1)	General	Age median (range): 64 (20-86) years Weight median (range): 72 (35-149) kg 451 (65%) male 468 (67%) in White 11 (1.6%) in Black 190 (27%) in Asian 25 (3.6%) in Other	
	Pediatrics (if any)	Not Applicable.	
Dose(s) Included		0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100 mg Q2W; 200 mg Q3W	
Exposure Metrics Explored (range)		The PK exposure metrics, including $C_{avg,\ first\ cycle}$, $C_{trough,first\ cycle}$ and $C_{max,first\ cycle}$, were derived from the population pharmacokinetic analysis for tarlatamab based on the model-predicted concentration-time profiles depending on the respective subjects dose, regimen, and PK covariates. These exposure metrics were comparable to steady state exposures.	
Covariates Evaluated		Age, body weight, sex, race, ethnicity, liver metastasis, brain metastasis, smoking status, number of prior lines of anticancer therapy, prior PD-1 or PD-L1 inhibitor theray, sum of target lesion diameters, presence of ADA, chronic kidney disease category (CKD) based on estimated glomercular filtration rate, National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic dysfunction.	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		Cox regression model: PFS, OS, DOR Emax model: ORR, DCR Imax model: BTSR	**Yes**

Model Parameter Estimates	Tables 2 to 5 of Amgen Pharmacometrics Report 160173	Yes
Model Evaluation	Base model selection was based on objective function value (OFV), Akaike information criterion (AIC), and/or Bayesian information criterion (BIC). Once the base model was determined and the ER relationship was identified as significant, a forward inclusion and backward elimination method was implemented to explore potential covariates that could significantly affect the ER relationship in a multivariate fashion.	Yes
Covariates and Clinical Relevance	Sum of target lesion diameters (baseline; independent of exposures) and mild/moderate hepatic impairment were found to be significantly associated with higher hazard for OS. Subgroups of the significant covariates identified in tarlatamab population PK analysis (Report 160172) were evaluated on efficacy. None of the covariates evaluated in this analysis resulted in clinically meaningful change in efficacy and therefore do not warrant a dose adjustment.	Yes
Simulation for Specific Population	Not applicable	
Visualization of E-R relationships	Figures 3 to 10 of Amgen Pharmacometrics Report 160173	Yes
Overall Clinical Relevance for ER	The results of ER analysis suggest that the proposed clinical regimen of 10 mg Q2W reaches the plateau of efficacy in this patient population	Yes

	(Figure 1 of Amgen Report 160173). None of the covariates evaluated in this analysis resulted in clinically meaningful change in efficacy and therefore do not warrant a dose adjustment.	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	There are no clinically significant exposure response relationships for efficacy over the exposure range observed between tarlatamab-dlle 10 mg and 100 mg (10 times the highest approved recommended dosage).	Yes

Amgen Pharmacometrics Report: 160173

Table 1. Summary of Demographics, Clinical Characteristics and Baseline Covariates

Variable	20160323 N = 258	20200491 N = 220	20210004 N = 216	Overall N = 694
Age (year)				
Mean (SD)	62 (8)	63 (9)	63 (9)	63 (9)
Median (Min-Max)	63 (32-80)	64 (34-82)	64 (20-86)	64 (20-86)
Weight (kg)				
Mean (SD)	76 (19)	74 (16)	72 (15)	74 (17)
Median (Min-Max)	74 (35-149)	72 (41-123)	71 (39-127)	72 (35-149)
Sex				
Male	145 / 258 (56%)	156 / 220 (71%)	150 / 216 (69%)	451 / 694 (65%)
Female	113 / 258 (44%)	64 / 220 (29%)	66 / 216 (31%)	243 / 694 (35%)
Race				
Caucasian	203 / 258 (79%)	138 / 220 (63%)	127 / 216 (59%)	468 / 694 (67%)
Black	9 / 258 (3.5%)	1 / 220 (0.5%)	1 / 216 (0.5%)	11 / 694 (1.6%)
Asian	26 / 258 (10%)	79 / 220 (36%)	85 / 216 (39%)	190 / 694 (27%)
Others	20 / 258 (7.8%)	2 / 220 (0.9%)	3 / 216 (1.4%)	25 / 694 (3.6%)
Ethnicity				
Hispanic	7 / 258 (2.7%)	3 / 220 (1.4%)	14 / 216 (6.5%)	24 / 694 (3.5%)
Non-Hispanic	251 / 258 (97%)	215 / 220 (98%)	201 / 216 (93%)	667 / 694 (96%)

Missing	0 / 258 (0%)	2 / 220 (0.9%)	1 / 216 (0.5%)	3 / 694 (0.4%)
ADA status				
Negative	236 / 258 (91%)	191 / 220 (87%)	179 / 216 (83%)	606 / 694 (87%)
Positive	22 / 258 (8.5%)	29 / 220 (13%)	37 / 216 (17%)	88 / 694 (13%)
Baseline sum of target lesion diameters (mm)				
Mean (SD)	93 (68)	104 (63)	80 (52)	92 (63)
Median (Min-Max)	80 (10-758)	91 (10-300)	68 (10-270)	80 (10-758)
Missing	1	0	0	1
Smoking status				
Never	22 / 256 (8.6%)	14 / 220 (6.4%)	23 / 216 (11%)	59 / 692 (8.5%)
Current	49 / 256 (19%)	33 / 220 (15%)	46 / 216 (21%)	128 / 692 (18%)
Former	185 / 256 (72%)	173 / 220 (79%)	147 / 216 (68%)	505 / 692 (73%)
Missing	2	0	0	2
Number of prior anticancer therapies				
NHXACTHR = 1	64 / 258 (25%)	4 / 220 (1.8%)	211 / 216 (98%)	279 / 694 (40%)
NHXACTHR = 2	120 / 258 (47%)	134 / 220 (61%)	5 / 216 (2.3%)	259 / 694 (37%)
NHXACTHR ≥ 3	72 / 258 (28%)	82 / 220 (37%)	0 / 216 (0%)	154 / 694 (22%)
Missing	2 / 258 (0.8%)	0 / 220 (0%)	0 / 216 (0%)	2 / 694 (0.3%)
Brain metastasis at screening				
No brain metastasis	185 / 258 (72%)	162 / 220 (74%)	118 / 216 (55%)	465 / 694 (67%)
Brain metastasis	73 / 258 (28%)	58 / 220 (26%)	98 / 216 (45%)	229 / 694 (33%)
Liver metastasis at screening				
No liver metastasis	142 / 258 (55%)	141 / 220 (64%)	157 / 216 (73%)	440 / 694 (63%)
Liver metastasis	116 / 258 (45%)	79 / 220 (36%)	59 / 216 (27%)	254 / 694 (37%)
Prior PD-1/PD-L1 administration				
No prior PD-1/PD-L1 admin	86 / 258 (33%)	57 / 220 (26%)	63 / 216 (29%)	206 / 694 (30%)
Prior PD-1/PD-L1 admin	172 / 258 (67%)	163 / 220 (74%)	153 / 216 (71%)	488 / 694 (70%)
Chronic kidney disease (CKD) stage at baseline				
Normal	145 / 258 (56%)	118 / 220 (54%)	101 / 216 (47%)	364 / 694 (52%)
Mild	89 / 258 (34%)	79 / 220 (36%)	90 / 216 (42%)	258 / 694 (37%)
Moderate	20 / 258 (7.8%)	22 / 220 (10%)	25 / 216 (12%)	67 / 694 (9.7%)
(Missing)	4 / 258 (1.6%)	1 / 220 (0.5%)	0 / 216 (0%)	5 / 694 (0.7%)
NCI-ODWG				
Normal	191 / 258 (74%)	157 / 220 (71%)	162 / 216 (75%)	510 / 694 (73%)
Mild or moderate	67 / 258 (26%)	63 / 220 (29%)	53 / 216 (25%)	183 / 694 (26%)
Missing	0 / 258 (0%)	0 / 220 (0%)	1 / 216 (0.5%)	1 / 694 (0.1%)

Table 2. Results of Cox Regression Analyses for PFS, OS and DOR

Response Variable	Predictor Variable	Estimate	Standard Error	P-value
Overall Survival, OS	$C_{avg, first\ cycle}$	0.862	0.0313	0.00000231
Progression Free Survival, PFS	$C_{avg, first\ cycle}$	0.927	0.0288	0.00853
Duration of Response, DOR	$C_{avg, first\ cycle}$	0.943	0.0648	0.361

Note: Hazard ratio can be estimated by exponentiating the parameter estimates for Cox regression analysis; Exposure metrics were evaluated as logarithm of values.

Table 3. Summary of multivariate Regression Analysis Results for PFS and OS

Response Variable	Predictor Variable	Estimate	Standard Error	P-value
Overall Survival, OS	$C_{avg, first\ cycle}$	0.875	0.0329	0.0000492
	Sum of tumor diameter (baseline)	1.00261	0.000552	0.00000223
	Mild hepatic dysfunction based on NCI criteria at baseline	1.50	0.122	0.000972
Progression Free Survival, PFS	$C_{avg, first\ cycle}$	0.938	0.0292	0.0291
	Sum of tumor diameter (baseline)	1.00335	0.000536	4.27E-10

$C_{avg, first\ cycle}$ = model-estimated averaged concentration over the first cycle; Exposure metrics were evaluated as logarithm of values.

Table 4. Summary of Univariate Analysis between $C_{avg, first\ cycle}$ and ORR/DCR

Univariate Analysis for ORR		
	Estimate	95% CI
Log-linear Model: AIC: 879.449 ; BIC: 888.534 ; OFV: 875.449		
β_0: Intercept of log odds	-1.50	[-2.14, -0.854]
β_1: Slope of log odds change with one unit increase of logarithm in $C_{avg, first\ cycle}$	0.113	[0.0235, 0.203]
Emax Model: AIC: 865.586 ; BIC: 874.671 ; OFV: 861.586		
E_{max}: maximum ORR from drug effect	0.370	[0.328, 0.414]
EC_{50}: $C_{avg, first\ cycle}$ (ng/mL) needed to achieve 50% of maximum ORR	54.3	[25.3, 116]
Univariate Analysis for DCR		
	Estimate	95% CI
Log-linear Model: AIC: 877.750 ; BIC: 886.835 ; OFV: 873.750		
Large correlation (-0.967) between parameter estimates was found between β_0 and β_1		
β_0: Intercept of log odds	-0.900	[-1.66, -0.141]
β_1: Slope of log odds change with one unit increase of logarithm in $C_{avg, first\ cycle}$	0.226	[0.115, 0.337]
Emax Model: AIC: 865.662 ; BIC: 874.747 ; OFV: 861.662		
E_{max}: maximum DCR from drug effect	0.727	[0.681, 0.769]
EC_{50}: $C_{avg, first\ cycle}$ (ng/mL) needed to achieve 50% of maximum DCR	47.0	[24.9, 88.6]

$C_{avg, first\ cycle}$ = model-estimated averaged concentration over the first cycle; ORR = objective response rate; DCR = disease control rate; AIC = Akaike information criterion; BIC = Bayesian information criterion; OFV = objective function value

Table 5. Summary of Regression Analysis Results for BTSR

Regression Analysis for BTSR		
	Estimate	95% CI
Log-linear Model: AIC: 5440.376 ; BIC: 5453.765 ; OFV: 5434.376		
Intercept	3.72	[-12.0, 19.4]
Slope for logarithm of $C_{avg, first\ cycle}$	-3.63	[-5.84, -1.42]
Imax Model : AIC: 5432.374 ; BIC: 5450.226 ; OFV: 5424.374		
β_0: baseline effect	27.8	[13.4, 57.7]
Imax: maximum inhibition from drug effect	53.3	[36.6, 77.7]
IC50: $C_{avg, first\ cycle}$ (ng/mL) needed to achieve 50% of maximum inhibition	37.4	[10.2, 138]

BTSR = Best tumor size reduction (% change from baseline); AIC = Akaike information criterion; BIC = Bayesian information criterion; OFV = objective function value.

Figure 1. Model Estimated Exposure-Response Relationships for ORR, DCR and percentage of subjects with Grade 3+ neutropenia events using pooled data from 20160323 and 20200491

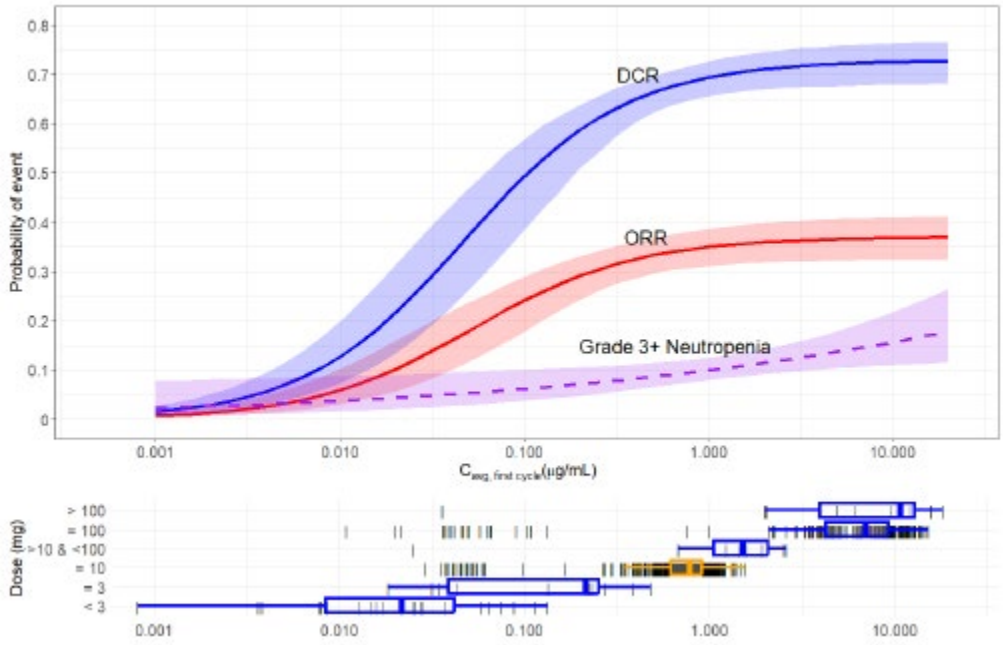


Figure 3. Kaplan–Meier Plot of Overall Survival Stratified by Model-predicted $C_{avg,\ first\ cycle}$ Quartiles

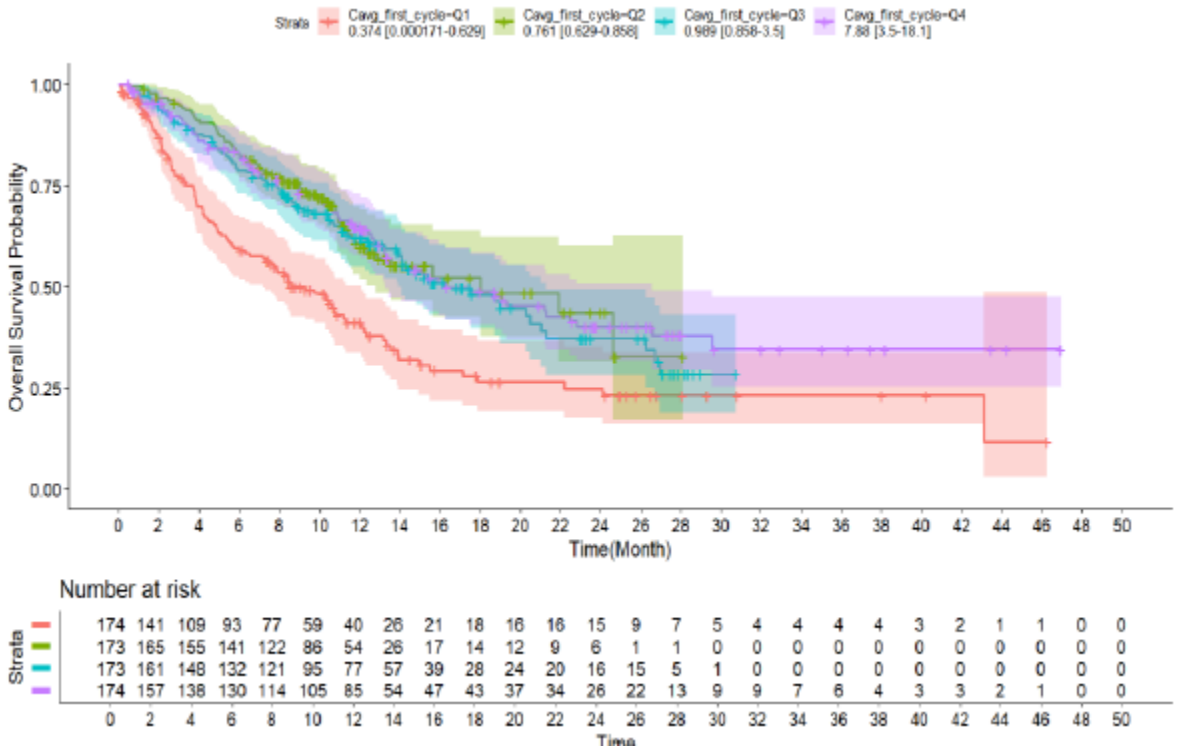


Figure 4. Kaplan-Meier Plot of Progression Free Survival Stratified by Model-predicted $C_{avg,\ first\ cycle}$ Quartiles

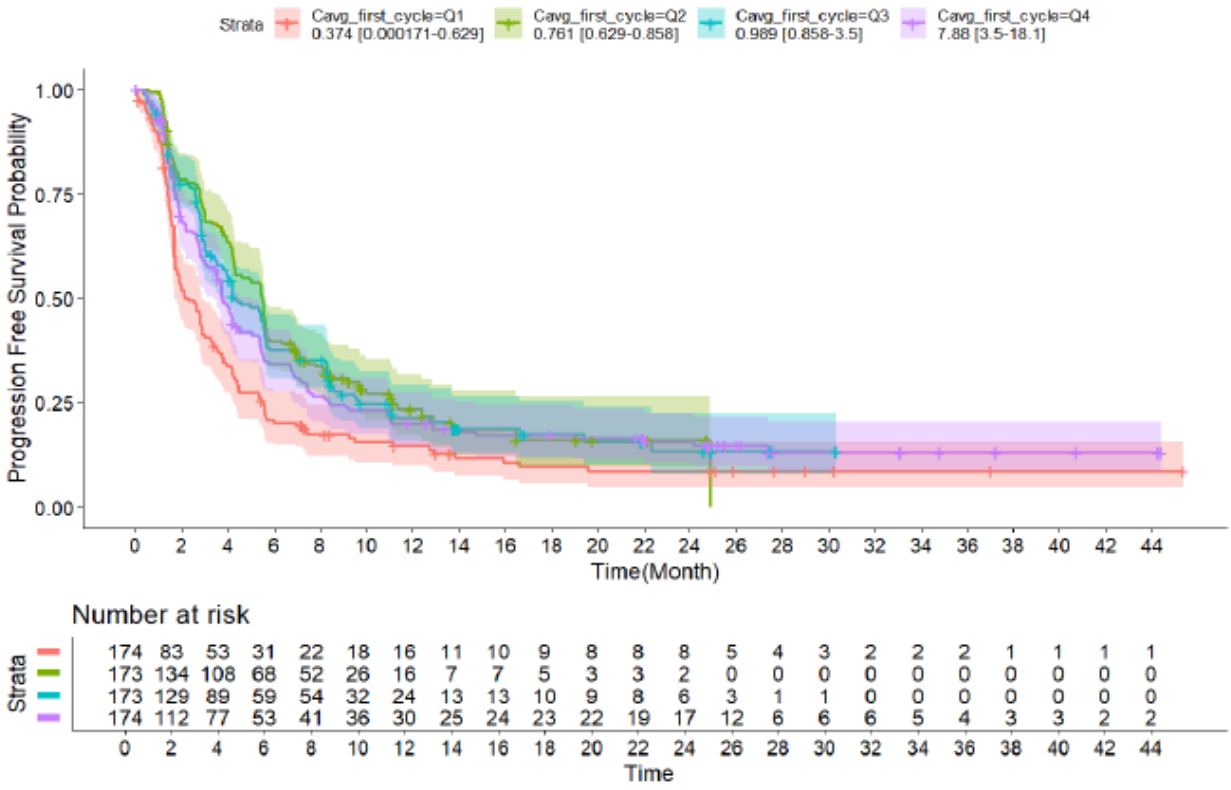


Figure 5. Kaplan–Meier Plot of Duration of Response (DOR) Stratified by $C_{avg,\ first\ cycle}$ Quartiles

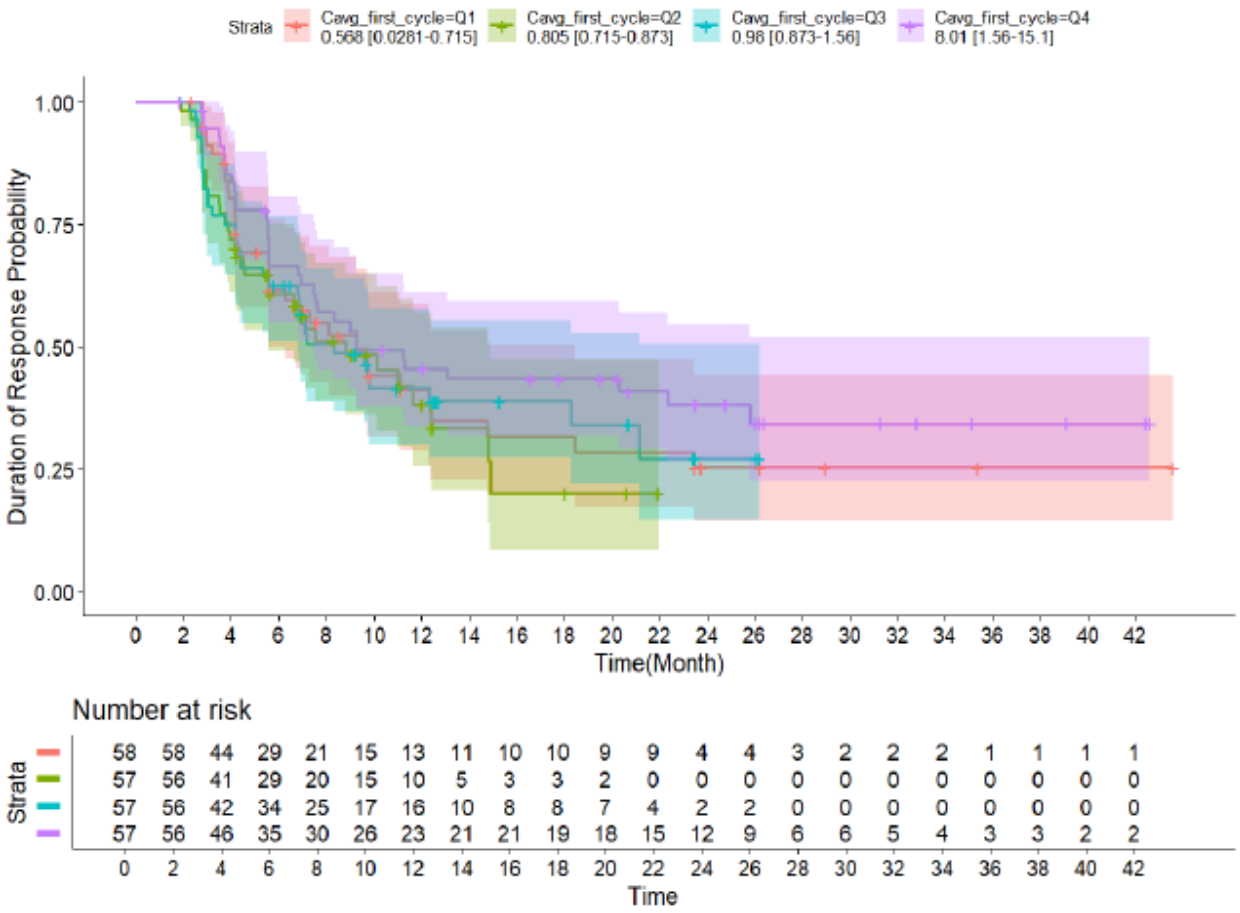


Figure 6. Relationships Between ORR and DCR vs. Model-predicted $C_{avg,\ first\ cycle}$ Quartiles

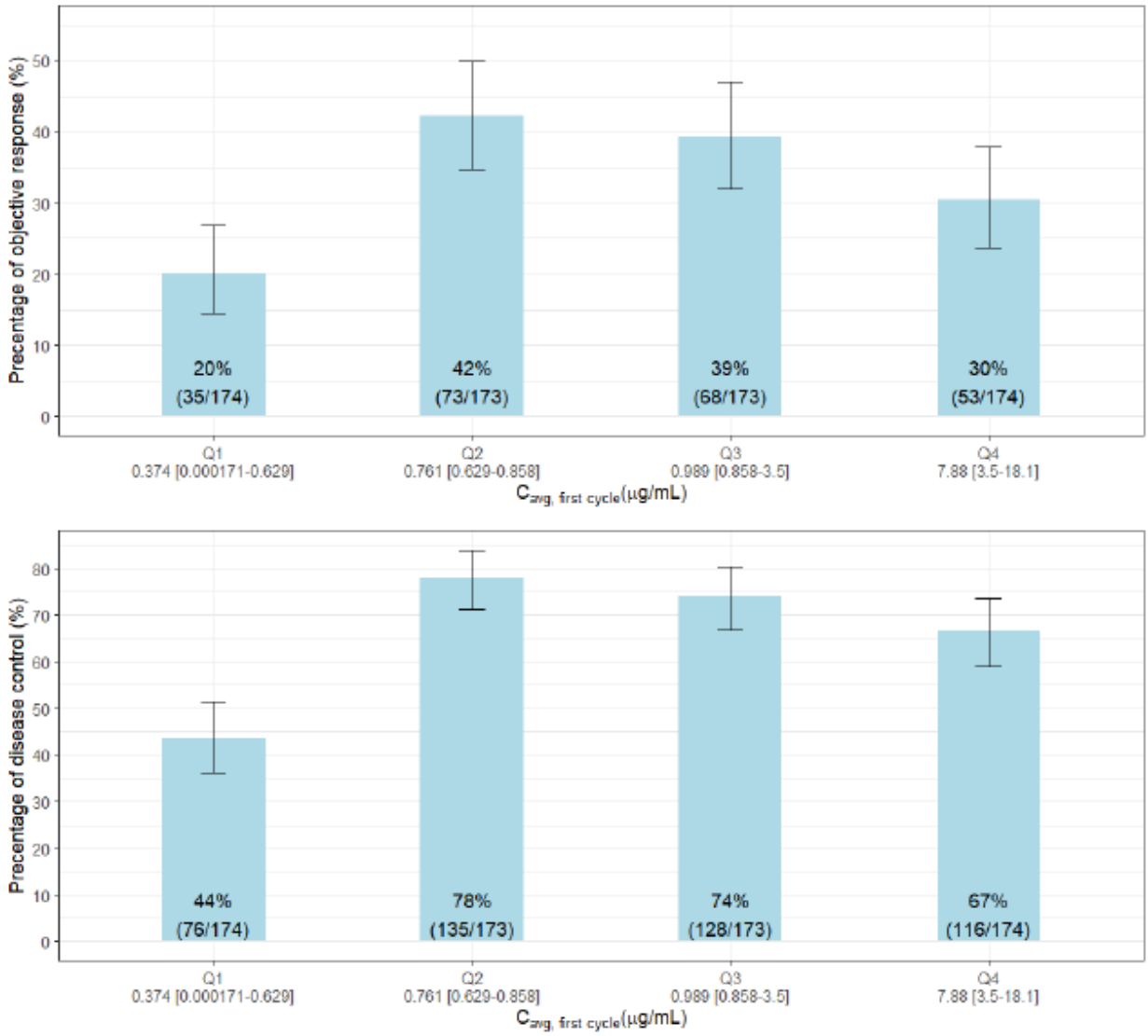


Figure 7. Best Tumor Size Response by Independent Assessor vs. Model-predicted tarlatamab $C_{avg,\ first\ cycle}$

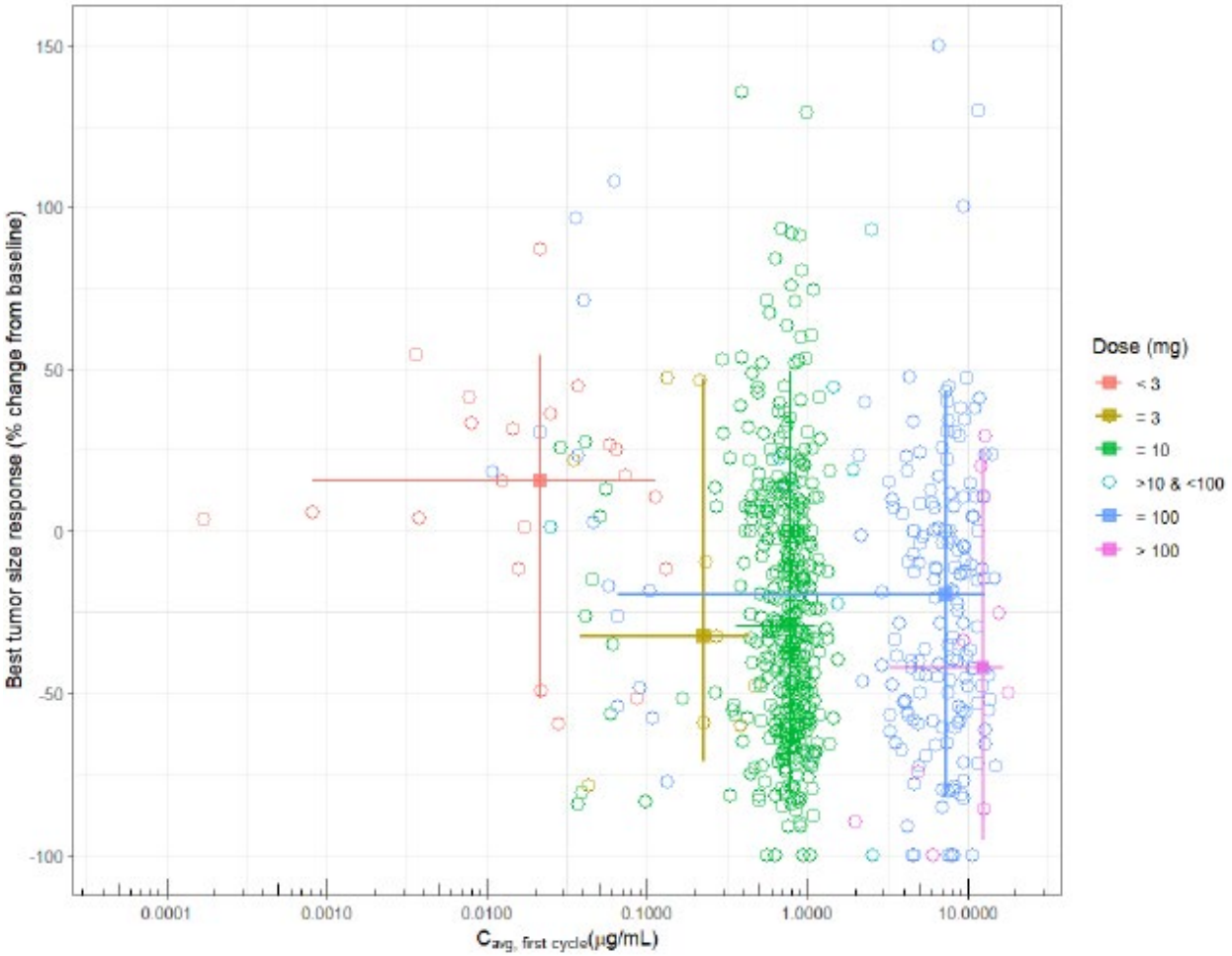


Figure 8. Model-Predicted ORR and Observed ORR by tarlatamab $C_{avg,\ first\ cycle}$ quartiles

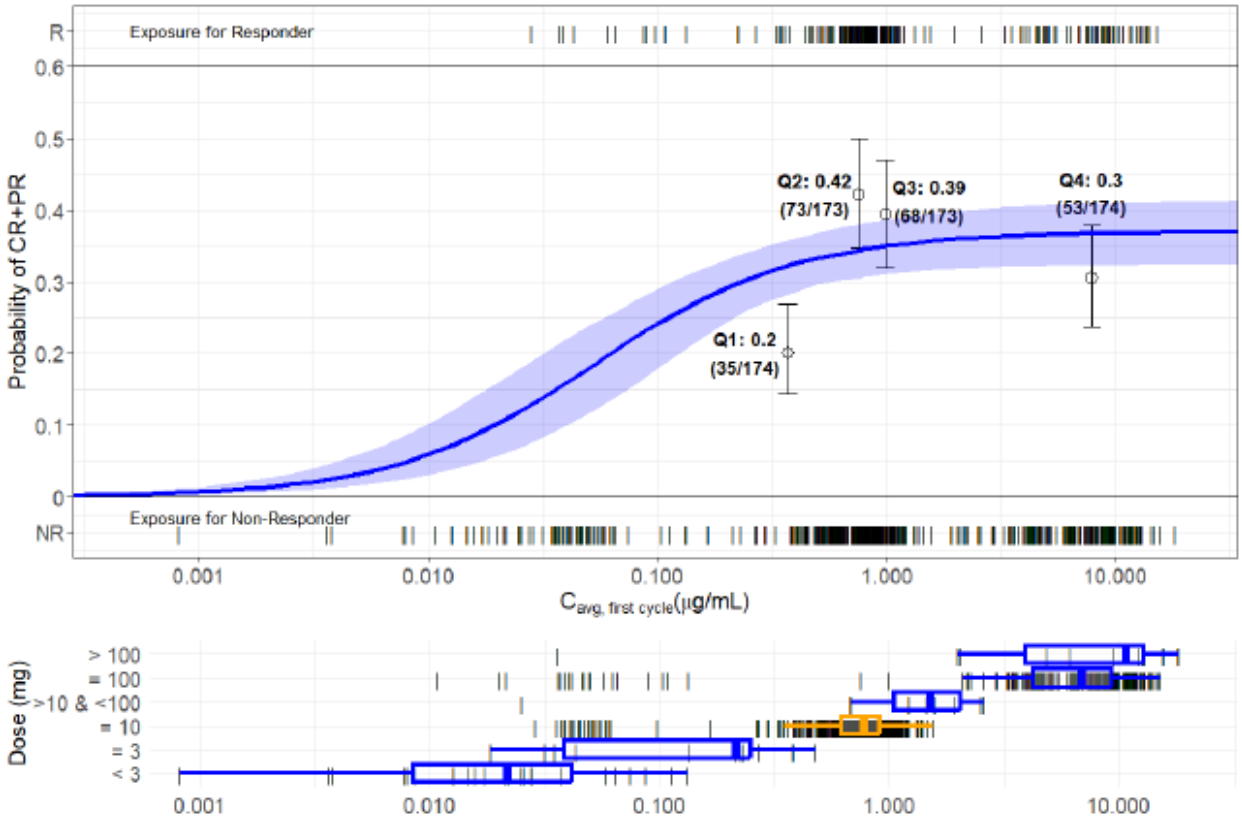


Figure 9. Model-predicted DCR and DCR distribution by tarlatamab $C_{avg,\ first\ cycle}$ quartiles

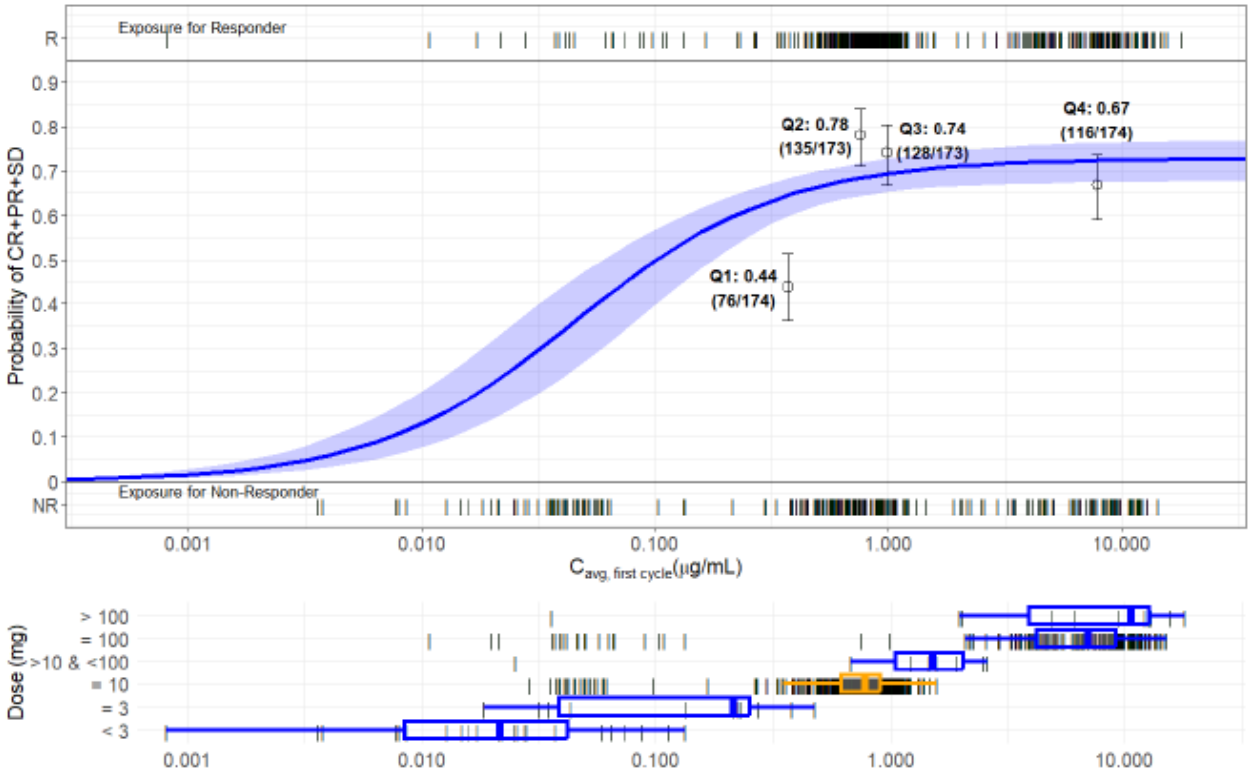
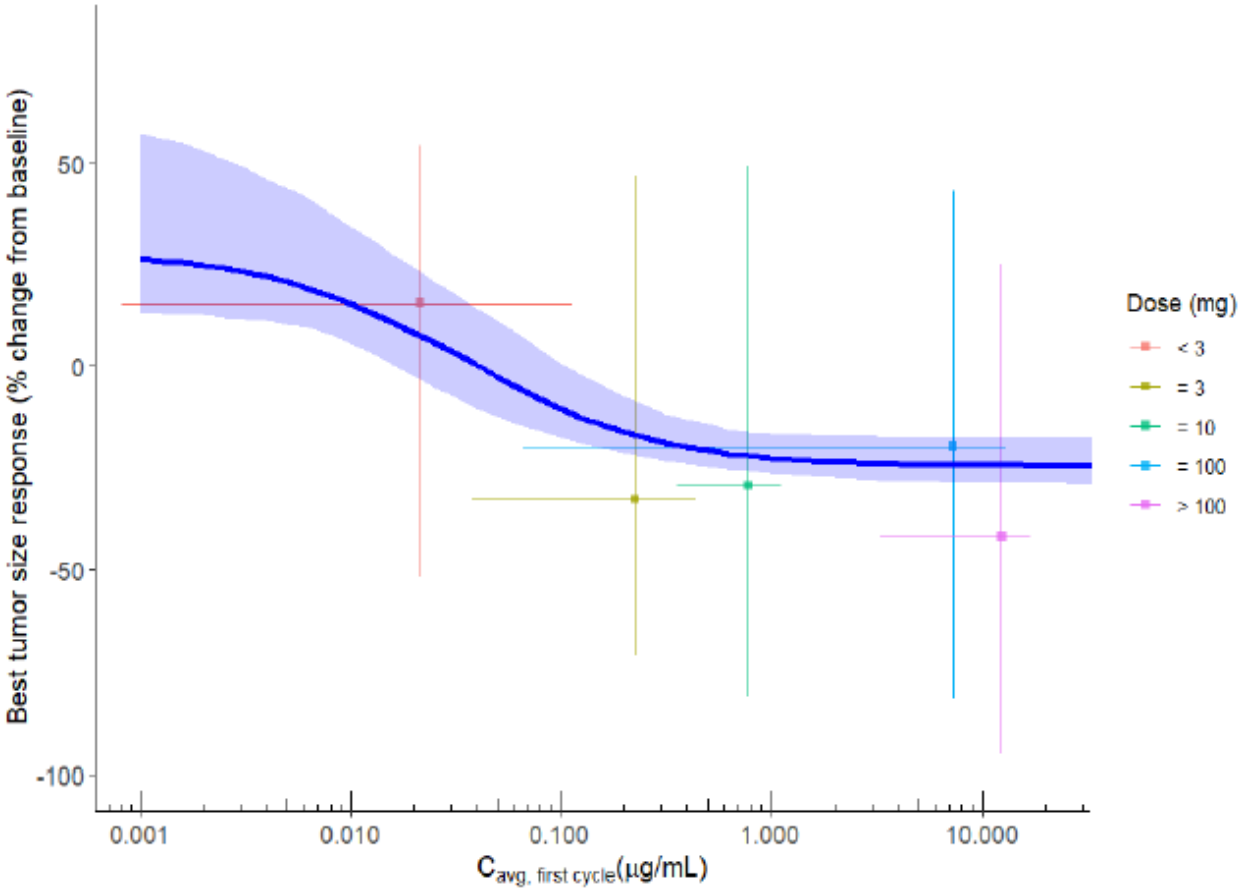


Figure 10. Model-simulated BTSR and Observed BTSR median (95%CI) and tarlatamab median (95%CI) $C_{avg,\ first\ cycle}$ by target dose group



19.4.3.3. ER (safety) Executive Summary

The FDA's Assessment:

Lack of exposure-safety (i.e., Gr≥3 TEAE/ICANS/CRS) was observed across exposures. Significant positive E-R relationship with shallow trend was observed for Gr≥3 neutropenia, with incremental changes for the probability of events at exposures of the target dose. Asian race presented an increased risk for Gr≥3 neutropenia, which is exposure independent and does not warrant a dosage adjustment for exposure difference of <20%.

19.4.3.4. ER (safety) Assessment Summary

The Applicant's Position:

No clear trends for exposure-response relationships were identified for grade ≥ 3 adverse events, grade ≥ 3 treatment-related adverse events, and grade ≥ 3 adverse events of interest of neurological toxicity including ICANS, and CRS. A statistically significant trend was observed for higher percentage of subjects experiencing grade ≥ 3 neutropenia with increasing tarlatamab exposures. A higher percentage of Asian subjects are estimated to have grade ≥ 3 neutropenia relative to Caucasian subjects. However, the risk of grade ≥ 3 neutropenia events was not associated with higher tarlatamab exposures.

The results of the exposure-response analysis suggest that the proposed clinical regimen of 10 mg Q2W reaches the plateau of efficacy with a limited impact on neutropenia and provides a reasonable balance of benefit-risk in this patient population. None of the covariates evaluated in this analysis resulted in clinically meaningful changes in the drug's effect on efficacy and therefore do not warrant a dose adjustment.

General Information		
Goal of ER analysis		Characterize relationships between tarlatamab serum exposures and key safety endpoints, including overall treatment-emergent adverse event (TEAE), treatment-related adverse event (TRAE) and selected TEAEs of interest, including neutropenia, neurological events including immune effector cell-associated neurotoxicity syndrome (ICANS), and cytokine release syndrome (CRS)
Study Included		The dataset for ER analyses consisted of 692 subjects with small cell lung cancer (SCLC) receiving at least one dose of tarlatamab in the monotherapy setting in the phase 1 Study 20160323, phase 2 Study 20200491, and phase 3 Study 20210004
Population Included		SCLC patients
Endpoint		Maximal grade of TEAE, TRAE, and Event of Interest: TEAE of neutropenia, neurological events including immune effector cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome (CRS).
No. of Patients (total, and with individual PK)		692
Population Characteristics (Table 1)	General	Age median (range): 64 (20-86) years Weight median (range): 72 (35-149) kg 451 (65%) male 468 (67%) in White

		11 (1.6%) in Black 190 (27%) in Asian 25 (3.6%) in Other	
	Organ impairment	Hepatic impairment (NCI-ODWG): Normal: 510 (73%), Mild or Moderate LD: 183 (26%) Renal impairment (CKD based on eGFR): Normal: 364 (52%), Mild: 258 (37%), Moderate: 67 (9.7%), Missing: 5 (0.7%)	
	Pediatrics (if any)	Not Applicable	
	Geriatrics (if any)	Age ≥ 75: n = 57 (8.21%)	
Dose(s) Included		0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100 mg Q2W; 200 mg Q3W	
Exposure Metrics Explored (range)		The exposure metrics, including $C_{avg,\ first\ cycle}$, $C_{trough,first\ cycle}$ and $C_{max,first\ cycle}$, were derived from the population pharmacokinetic analysis for tarlatamab based on the model-predicted concentration-time profiles depending on the respective subjects dose, regimen, and PK covariates.	
Covariates Evaluated		Age, body weight, sex, race, ethnicity, liver metastasis, brain metastasis, smoking status, number of prior lines of anticancer therapy, prior PD-1 or PD-L1 inhibitor theray, sum of target lesion diameters, presence of ADA, chronic kidney disease category (CKD) based on estimated glomercular filtration rate, National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic dysfunction.	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		Logistic regression: Grade 3+ TEAE, Grade 3+ TRAE, Grade 3+ TEAE of neutropenia, neurological event including ICANS, CRS, and neutropenia	**Yes**

Model Parameter Estimates	Table 7 of Amgen Pharmacometrics Report: 160173	Yes
Model Evaluation	ER relationships were assessed by Wald test. Associations were considered significant if the p-value was less than 0.05. When an ER relationship for a safety endpoint was identified to be significant, a stepwise method was implemented to identify potential covariates based on BIC.	Yes
Covariates and Clinical Relevance	A statistically significant trend was observed for higher percentage of subjects experiencing grade ≥ 3 neutropenia with increasing tarlatamab exposures. A higher percentage of Asian subjects are estimated to have grade ≥ 3 neutropenia relative to Caucasian subjects. However, the risk of grade ≥ 3 neutropenia events was not associated with higher tarlatamab exposures.	Yes
Simulation for Specific Population	Not Applicable	
Visualization of E-R relationships	Figures 12 and 13 of Amgen Pharmacometrics Report: 160173	Yes
Overall Clinical Relevance for ER	Tarlatamab exposure was associated with Grade 3+ neutropenia. No covariate was found to be significant for Grade 3+ neutropenia.	Yes
Labeling Language	**Description**	**Acceptability** **[FDA's comments]**

12.2 Pharmacodynamics	There is an exposure response relationship between tarlatamab-dlle exposure and neutropenia or neurologic toxicity including ICANS with a higher risk of any grade neutropenia or neurologic toxicity including ICANS at higher exposure.	Yes

Amgen Pharmacometrics Report: 160173

Table 7. Results of Logistic Regression Analyses for Safety Events

Safety Event	Predictor Variable	Estimate	Standard Error	P-value
Grade ≥3 TEAE	$C_{avg,\ first\ cycle}$	-0.00207	0.0488	0.966
Grade ≥3 TRAE	$C_{avg,\ first\ cycle}$	0.0566	0.0512	0.269
Grade ≥3 Neutropenia	$C_{avg,\ first\ cycle}$	0.225	0.0875	0.0101
Grade ≥3 Neurologic toxicity including ICANS	$C_{avg,\ first\ cycle}$	0.0123	0.0842	0.884
Grade ≥3 CRS	$C_{avg,\ first\ cycle}$	-0.394	0.113	0.000460
Grade ≥3 CRS	$C_{max,\ first\ cycle}$	-0.368	0.114	0.00129

TEAE = Treatment Emergent Adverse Event; TRAE = Treatment Related Adverse Event; ICANS = immune effector cell-associated neurotoxicity syndrome; CRS = cytokine release syndrome. ln = natural log. As a logistic regression result for grade ≥ 3 CRS with $C_{max,\ first\ cycle}$ is also provided.Exposure metrics were evaluated as logarithm of values.

Figure 11. Proportion of subjects experiencing Grade 3+ Safety events by Tarlatamab Exposure Quartiles

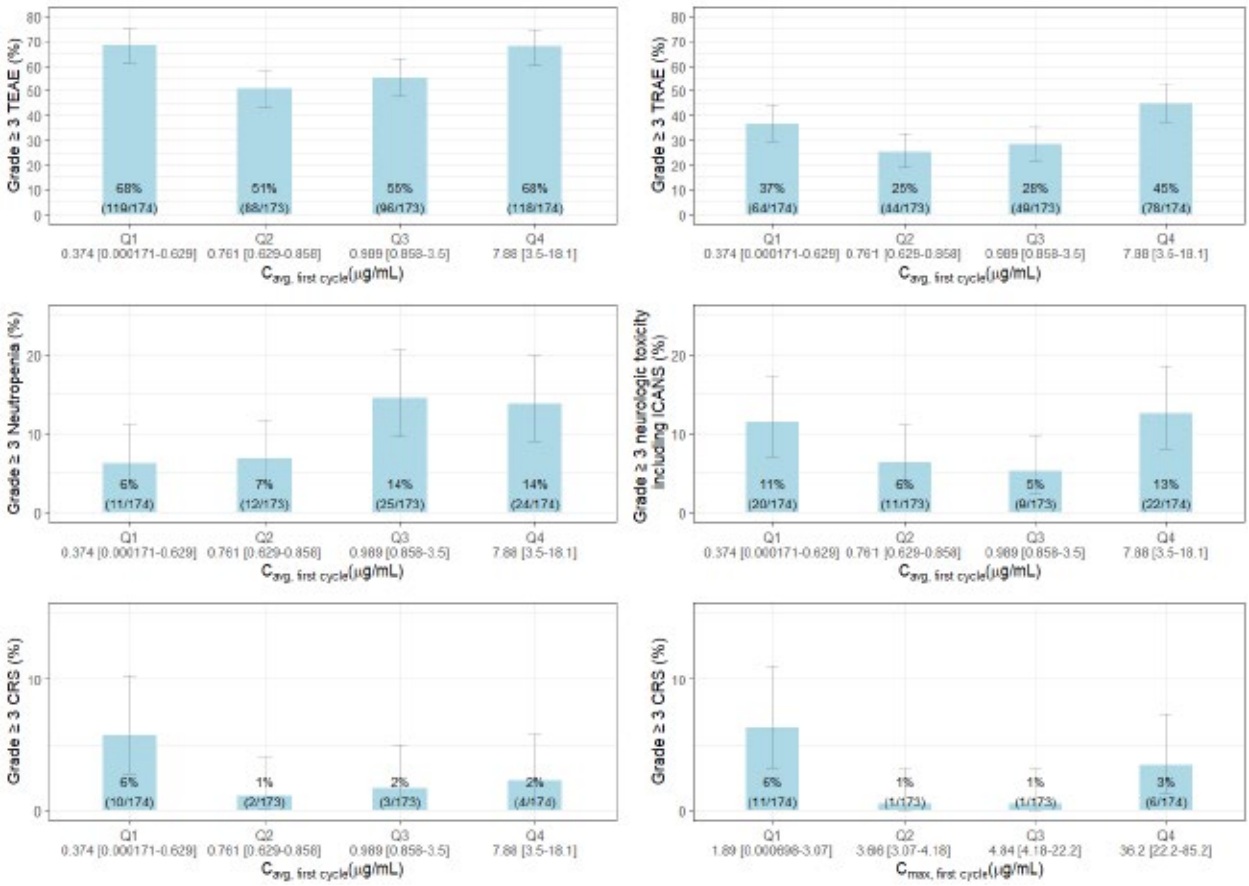
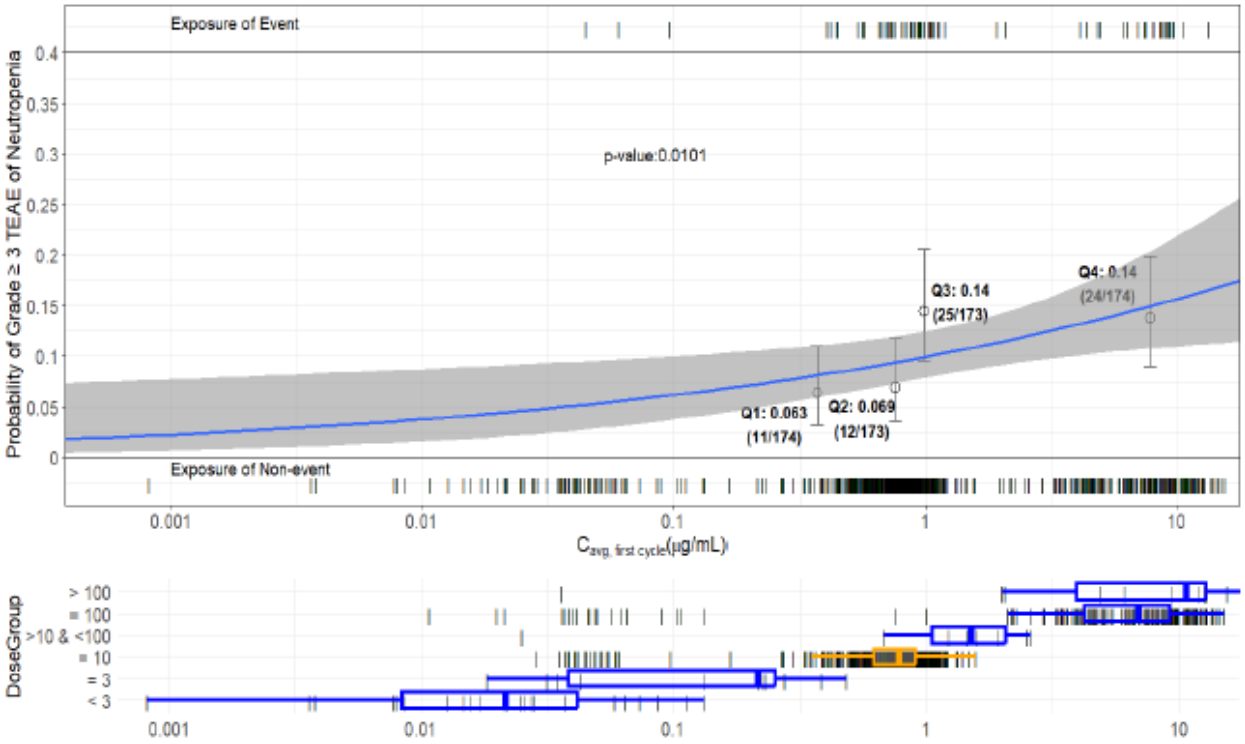


Figure 12. Model Predicted Probability of Grade 3+ neutropenia and Observed Grade 3+ neutropenia events versus tarlatamab $C_{avg,\ first\ cycle}$



The FDA's Assessment:

The E-R relationships for efficacy and safety are generally consistent with the previous E-R analyses (refer to multi-discriplinary review of BLA761344), supporting the proposed recommended dosages.

19.4.3.5. ER Review Issues

None.

19.4.3.6. Reviewer's Independent Analysis

None.

19.4.3.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

No clear trends for exposure-response relationships were identified for grade ≥ 3 adverse events, grade ≥ 3 treatment-related adverse events, and grade ≥ 3 adverse events of interest of neurological toxicity including ICANS, and CRS. A statistically significant trend was observed

for higher percentage of subjects experiencing grade ≥ 3 neutropenia with increasing tarlatamab exposures. A higher percentage of Asian subjects are estimated to have grade ≥ 3 neutropenia relative to Caucasian subjects. However, the risk of grade ≥ 3 neutropenia events was not associated with higher tarlatamab exposures.

The results of the exposure-response analysis suggest that the proposed clinical regimen of 10 mg Q2W reaches the plateau of efficacy with a limited impact on neutropenia and provides a reasonable balance of benefit-risk in this patient population. None of the covariates evaluated in this analysis resulted in clinically meaningful changes in the drug's effect on efficacy and therefore do not warrant a dose adjustment.

The FDA's Assessment:
FDA agree with the Applicant's position. The benefit risk ratio based on E-R analyses for the proposed recommended dosage for 2L+ SCLC remains consistent with the previous review.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Not applicable.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Zhe Li, PhD	CDER/OTS/OCP/DCPII	Sections: 6.2.3, 19.4.1	**Select one:** _X_Authored ___Approved
	Signature: ZHE LI -S Digitally signed by ZHE LI -S Date: 2025.11.13 12:35:11 -05'00'			
Clinical Pharmacology Team Leader	Stacy Shord, PharmD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** __Authored _X_Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S Date: 2025.11.13 14:20:59 -05'00'			
Clinical Pharmacology/ Pharmacometrics Team Leader	Ye Xiong, PhD	CDER/OTS/OCP/DPM	Sections:6, 19.4	**Select one:** ___Authored _X_Approved
	Signature: YE XIONG -S Digitally signed by YE XIONG -S Date: 2025.11.13 12:52:56 -05'00'			
Clinical Pharmacology/ Pharmacometrics Reviewer	Jiang Liu, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** _X_Authored ___Approved
	Signature: JIANG LIU -S Digitally signed by JIANG LIU -S Date: 2025.11.13 12:49:57 -05'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** ___Authored _X_Approved
	Signature: NAM A. RAHMAN -S Digitally signed by NAM A. RAHMAN -S Date: 2025.11.13 12:11:26 -05'00'			

Assessment Aid Signature Page (BLA 761344/S-001)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Yufan Liu, MD	CDER/ OND/OOD/DOII	Sections: All	**Select one:** _X_Authored ___Approved
	Signature: Erin Larkins to sign on behalf of Yufan Liu. ERIN A. LARKINS -S Digitally signed by ERIN A. LARKINS -S Date: 2025.11.13 15:07:45 -05'00'			
Clinical Reviewer	Jeannette Nashed, BSN, MSN, CRNP	CDER/ OND/OOD/DOII	Sections: 1, 8, 13	**Select one:** _X_Authored ___Approved
	Signature: JEANNETTE C. NASHED -S Digitally signed by JEANNETTE C. NASHED -S Date: 2025.11.13 12:39:33 -05'00'			
Clinical Team Leader	Justin Malinou, MD	CDER/OND/OOD/DOII	Sections: All	**Select one:** _X_Authored _X_Approved
	Signature: See signature in DARRTS.			
Cross-Disciplinary Team Leader (CDTL)	Justin Malinou, MD	CDER/OND/OOD/DOII	Sections: All	**Select one:** _X_Authored _X_Approved
	Signature: See signature in DARRTS.			
Division Director	Erin Larkins, MD	CDER/OND/OOD/DOII	Sections: All	**Select one:** _X_Approved
	Signature: See signature in DARRTS.			

Assessment Aid Signature Page (BLA 761344/S-001)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Lang Li, PhD	CDER/OTS/OB/DBV	Sections: 1, 7, 8	**Select one:** _X_ Authored ___ Approved
	Signature: Flora Mulkey to sign on behalf of Lang Li. Flora M. Mulkey -S Digitally signed by Flora M. Mulkey -S Date: 2025.11.13 12:21:46 -05'00'			
Statistical Team Leader	Flora Mulkey, MS	CDER/OTS/OB/DBV	Sections: 1, 7, 8	**Select one:** _X_ Authored _X_ Approved
	Signature: Flora M. Mulkey -S Digitally signed by Flora M. Mulkey -S Date: 2025.11.13 12:22:19 -05'00'			
Supervisory Mathematical Statistician	Anup Amatya, PhD	CDER/OTS/OB/DBV	Sections: 1, 7, 8	**Select one:** ___ Authored _X_ Approved
	Signature: ANUP K. AMATYA -S Digitally signed by ANUP K. AMATYA -S Date: 2025.11.13 12:18:06 -05'00'			
Associate Director for Labeling (ADL)	Barbara Scepura, MSN	CDER/OND/OOD/DOII	Sections: 11	**Select one:** _X_ Authored ___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2025.11.13 13:04:56 -05'00'			

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ERIN A LARKINS
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761344Orig1s001

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 10, 2025

To: Ashley Lane, MS, Senior Regulatory Project Manager
Division of Oncology 2 (DO2)

Barbara Scepura, Associate Director for Labeling, DO2

From: Adesola Adejuwon, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, MS, RN, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for IMDELLTRA® (tarlatamab-dlle) for injection, for intravenous use

BLA: 761344, S-001

Background:
In response to DO2's consult request dated June 25, 2025, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for supplement 001 for IMDELLTRA® (tarlatamab-dlle) for injection, for intravenous use (Imdelltra). This supplement proposes to fulfill PMR 4635-1 and PMR 4635-2, and to convert the currently approved indication from accelerated approval to traditional approval based on efficacy results from Study 20210004, entitled "A Randomized,Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Subjects With Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy (DeLLphi-304)."

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on November 10, 2025, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on November 7, 2025.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at 240 402 5773 or Adesola.Adejuwon@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 7, 2025
To:	Ashley Lane, MS Senior Regulatory Health Project Manager **Division of Oncology II (DO2)**
Through:	Barbara Fuller, MSN, BSN, RN Team Lead, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adesola Adejuwon, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	IMDELLTRA (tarlatamab-dlle)
Dosage Form and Route:	for injection, for intravenous use
Application Type/Number:	BLA 761344
Supplement Number:	S-001
Applicant:	Amgen Inc.

1 INTRODUCTION

On June 18, 2025, Amgen Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved Biologics License Application (BLA) 761344/ S-001 for IMDELLTRA (tarlatamab-dlle) for injection. With this submission, the Applicant proposes to fulfill Postmarketing Requirement (PMR) 4635-1 and PMR 4635-2, and to convert the currently approved indication from accelerated approval to traditional approval based on efficacy results from Study 20210004, entitled "A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Subjects With Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy (DeLLphi-304)."

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on June 25, 2025 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for IMDELLTRA (tarlatamab-dlle) for injection.

2 MATERIAL REVIEWED

- Draft IMDELLTRA (tarlatamab-dlle) for injection MG received on June 18, 2025, and received by DMPP and OPDP on November 5, 2025.
- Draft IMDELLTRA (tarlatamab-dlle) for injection Prescribing Information (PI) received on June 18, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 5, 2025.
- Approved IMDELLTRA (tarlatamab-dlle) for injection labeling dated May 16, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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LAURIE J BUONACCORSI
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ADESOLA F ADEJUWON
11/07/2025 01:48:21 PM

BARBARA A FULLER
11/07/2025 01:55:46 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 19, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	BLA 761344/S-001
Product Name, Dosage Form, and Strength:	Imdelltra (tarlatamab-dlle) for injection, 1 mg/vial and 10 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Amgen Inc.
FDA Received Date:	June 18, 2025
TTT ID #:	2025-15237
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD, M.S.
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 INTRODUCTION

Amgen Inc. submitted an Efficacy Supplement for Imdelltra (tarlatamab-dlle) for injection to support the conversion of the accelerated approval granted on May 16, 2024, to full approval [redacted] (b) (4) .

Subsequently, the Division of Oncology 2 (DO2) requested that we review the proposed Imdelltra Prescribing Information (PI), Medication Guide (MG), container label(s), and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

We evaluated the proposed Imdelltra container labels, IV Solution Stabilizer container label, and carton labeling, and noted that the trademark "TM" symbol has been updated to registered ® symbol next to the proprietary name. We find this proposed change acceptable from a medication error perspective.

We evaluated the proposed Imdelltra Medication Guide and determined that it is acceptable from a medication error perspective.

However, the proposed Imdelltra Prescribing Information (PI), may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Oncology 2 (DO2) in Section 4.

4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Section 2 Dosage and Administration

a. In Table 12. *Maximum Storage Time* in Section 2.6 Preparation, consider revising the proposed language regarding the infusion instructions for refrigerated IMDELLTRA infusion bag to appear as a separate bullet and to read as follows for improved clarity:

For example:

Table 12. Maximum Storage Time for Prepared IMDELLTRA Infusion Bag

	Room Temperature 20°C to 25°C (68°F to 77°F)	Refrigerated 2°C to 8°C (36°F to 46°F)
Prepared IMDELLTRA Infusion Bag	8 hours	7 days
• Discard the prepared IMDELLTRA infusion bag after maximum storage time (from time of reconstitution). • If refrigerated, allow the prepared IMDELLTRA infusion bag to come to room temperature prior to administration, and complete the infusion (b) (4) (b) (4) (b) (4) within 8 hours (including preparation and infusion time). • Do not re-refrigerate prepared infusion bag.		

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Imdelltra received on June 18, 2025 from Amgen Inc..

Table 2. Relevant Product Information for Imdelltra	
Initial Approval Date	May 16, 2024
Nonproprietary Name	tarlatamab-dlle
Indication	*Approved:* For the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy. (b) (4)
Dosage Form	for injection
Strength	1 mg/vial and 10 mg/vial
Route of Administration	intravenous
Dose and Frequency	1 mg on Day 1 followed by 10 mg on Days 8, 15, and every 2 weeks thereafter. Treat patients until disease progression or unacceptable toxicity.
How Supplied	Sterile, single dose, preservative free white to slightly yellow, lyophilized powder supplied as follows: • 1 mg package (NDC 55513-059-01) includes 1 single-dose vial of 1 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer. • 10 mg package (NDC 55513-077-01) contains 1 single-dose vial of 10 mg IMDELLTRA and 2 vials of 7 mL IV Solution Stabilizer.
Storage	Store IMDELLTRA and IV Solution Stabilizer vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze. IMDELLTRA and IV Solution Stabilizer (IVSS) vials may be kept at room temperature between 20°C to 25°C (68°F to 77°F) for up to 24 hours in the original carton to protect from light.
Container Closure	(b) (4) glass vial with a 13 mm elastomeric stopper (b) (4) and an aluminum seal flip-of cap.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Imdelltra labels and labeling submitted by Amgen Inc..

- Prescribing Information received on June 18, 2025, available from \\CDSESUB1\EVSPROD\bla761344\0094\m1\us\114-labeling\draft\annotated\d-imdelltra-us-pi-v2-2l-indication-r-2025-xxxx.docx
- Medication Guide received on June 18, 2025, available from \\CDSESUB1\EVSPROD\bla761344\0094\m1\us\114-labeling\draft\annotated\d-imdelltra-us-mg-v2-2l-indication-r-2025-xxxx.docx
- Container label(s) received on June 18, 2025
- Carton labeling received on June 18, 2025

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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APPENDIX C. PREVIOUS DMEPA REVIEWS

On September 15, 2025, we searched for previous DMEPA reviews relevant to this current review using the terms, BLA 761344. Our search identified 2 previous reviews[b,c,] and we considered our previous recommendations to see if they are applicable for this current review.

APPEARS THIS WAY ON ORIGINAL

[b] Beniesfahany, F. Review of Revised Label and Labeling for Imdelltra (BLA 761344). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAY 02. TTT ID No.: 2023-6460-1.

[c] Beniesfahany, F. Human Factors Study Report and Label and Labeling Review for Imdelltra (BLA 761344). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAR 06. TTT ID: 2023-6728, 2023-6460.

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Clinical Inspection Summary

Date	September 10, 2025
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Kassa Ayalew, MD, MPH, Division Director Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Yufan Liu, Clinical Analyst Erin Larkins, MD, Division Director Division of Oncology 2 (DO2), Office of Oncology Products
BLA #	BLA 761344/S01
Applicant	Amgen Inc.
Drug	Tarlatamab-dlle (IMDELLTRA)
NME (Yes/No)	No
Therapeutic Classification	Bispecific T-cell engager (BiTE) monoclonal antibody
Proposed Indication(s)	(b) (4)
Consultation Request Date	July 02, 2025
Summary Goal Date	September 18, 2025
Action Goal Date	October 18, 2025
PDUFA Date	December 18, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 20210004 (DeLLphi-304) were submitted to the Agency in support of supplemental Biologics License Application (BLA) 761344/S01 to fulfill Post-Market Requirement (PMR) 4635-2 and to support the conversion of tarlatamab from accelerated approval to regular approval (b) (4) The Sponsor, Amgen Inc., was inspected.

The inspection of Amgen was conducted due to deficiencies identified at a clinical site in South Korea (Site #57002) during the original BLA review cycle in 2024 (see clinical inspection summary filed March 26, 2024) which included eligibility violations and underreporting of adverse events in the majority of enrolled patients. Based on these deficiencies and the current supplement, FDA issued an information request on July 15, 2025, requiring 100% source data verification at specified sites for Study DeLLphi-304. Amgen responded on July 28, 2025, asserting that comprehensive data verification activities had been performed at all study sites prior to the Primary Analysis.

The sponsor inspection did not reveal significant concerns regarding study conduct, data integrity, Good Clinical Practice (GCP), or regulatory compliance. The inspection verified that Amgen had implemented enhanced data oversight measures as outlined in their information request response. Amgen's oversight of Study DeLLphi-304 appears adequate.

Based on this inspection, Study DeLLphi-304 appears to have been conducted adequately, with the data submitted by the Applicant appearing acceptable in support of the proposed indication.

II. BACKGROUND

Amgen Inc. submitted BLA 761344/S01 containing results from a phase 3, randomized study (DeLLphi-304; 20210004) comparing tarlatamab to standard of care (SOC) to fulfill PMR 4635-2 and to support the conversion of tarlatamab from accelerated approval to regular approval (b) (4) .

Tarlatamab is a bispecific DLL3-directed CD3 T-cell engager that binds to DLL3 on the surface of tumor cells and CD3 on the surface of T-cells. Tarlatamab received accelerated approval on May 16, 2024, for the above indication.

Study DeLLphi-304 is an open-label, randomized, multi-center, phase 3 study evaluating tarlatamab versus SOC chemotherapy in SCLC patients who progressed after one prior platinum-containing therapy.

The study included a 21-day screening period, treatment period, safety follow-up visit, and long-term follow-up. Eligible subjects were randomized 1:1 to receive tarlatamab or SOC chemotherapy (lurbinectedin or topotecan in the US, Canada, Australia, Singapore, and Korea; amrubicin in Japan).

Randomization was stratified by prior anti-PD-1/PD-L1 exposure, chemotherapy-free interval (≥180 days; 90-180 days; <90 days), brain metastases presence, and standard of care (topotecan/amrubicin vs lurbinectedin).

Tarlatamab was administered as a 60-minute IV infusion with step dosing: 1 mg on cycle 1 day 1, then 10 mg on cycle 1 days 8 and 15, and every 2 weeks thereafter in 21-day cycles. Chemotherapy was administered per local standard dosing in 21-day cycles. Treatment continued until disease progression per RECIST 1.1, unacceptable toxicity, consent withdrawal, death, or study end.

The primary objective was comparing overall survival (OS). Key secondary objectives included progression-free survival (PFS), overall response rate (ORR), and duration of response (DOR) per RECIST 1.1.

Baseline assessments were performed within 21 days of enrollment. Pre-infusion assessments were required on all tarlatamab dosing days. Imaging included chest, abdomen, pelvis, and other

known sites. Brain MRI was performed at screening, then every 6 weeks (weeks 1-48), then every 12 weeks until progression, consent withdrawal, or new anticancer therapy. Follow-up included a safety visit ~60 days post-treatment, then survival follow-up every 12 weeks for up to 3 years after last enrollment or 1 year from last dose, whichever was later.

At data cut-off (January 29, 2025), 509 participants were randomized (254 tarlatamab, 255 SOC) across 31 countries, including 27 US subjects across 12 centers.

III. RESULT

Amgen Inc.
1 Amgen Center Drive
Thousand Oaks, CA 91329

Inspection dates: August 4 – 7, 2025.

This inspection assessed Amgen's oversight responsibilities for Study DeLLphi-304. Amgen was last inspected in September 2023.

The inspection of Amgen was conducted in part due to deficiencies identified during the FDA inspection of Site #57002 (Dr. Myung-Ju Ahn, Seoul, South Korea) for the original BLA, which included eligibility violations and underreporting of adverse events in the majority of enrolled subjects. Because of these findings and prompted by the current submission, FDA issued an information request on July 15, 2025, requesting that Amgen perform 100% source data review (SDR) and source data verification (SDV) of subject eligibility and adverse events at specified sites for Study DeLLphi-304.

Amgen provided their response on July 28, 2025, asserting that 100% SDR/SDV of subject eligibility and adverse events had been performed at all Study DeLLphi-304 sites prior to the Primary Analysis. The sponsor indicated that the data provided for Study DeLLphi-304 in the supplemental BLA included comprehensive data verification activities across all study sites.

Documents reviewed during this inspection included, but were not limited to, the firm's organizational charts, standard operating procedures, electronic data capture systems, personnel records, third-party agreements, protocol deviations, site monitoring activities, safety/adverse event reporting, data and safety oversight, records retention, and investigational product accountability. No significant issues were noted.

Monitoring files for three clinical sites from different geographic regions were reviewed in depth for compliance: Site #11126, Dr. Antonio Lugini (Italy); Site #73044, Dr. Jing Zhang (China); and Site #68414, Dr. Umut Demirci (Turkey). No significant deficiencies were noted.

The inspection examined documentation and audit trails to substantiate Amgen's claims regarding the comprehensive data verification activities. The inspection confirmed that, as per

their July 28, 2025, response to the July 15, 2025, FDA information request, Amgen had implemented enhanced data oversight measures for Study DeLLphi-304, with monitoring records and quality assurance documentation demonstrating that the committed data verification processes were completed across the global study sites.

The inspection did not reveal any issues related to safety/adverse event handling or reporting for the DeLLphi-304 study.

Based on the results of the inspection, Amgen's overall oversight of the study and monitoring of the clinical investigators appear adequate, thereby supporting the integrity of the data submitted in the supplemental BLA.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

Michele Fedowitz, M.D.
Team Leader
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Office of Scientific Investigations

CONCURRENCE: {*See appended electronic signature page}*

Kassa Ayalew, M.D.
Division Director
Division of Clinical Compliance Evaluation
Office of Scientific Investigation

CC:
Review Division /Project Manager/Ashley Lane
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-sBLA

Meeting Date and Time: May 16, 2025; 12:00 PM – 1:00 PM EDT
Meeting Location: Virtual Face-to-Face

Application Number: IND 134859
Product Name: IMDELLTRA (tarlatamab, AMG 757)
Indication: (b) (4)
Sponsor Name: Amgen Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Justin Malinou, MD

FDA ATTENDEES (tentative)
Erin Larkins, MD, Acting Director, Division of Oncology 2 (DO2)
Justin Malinou, MD, Acting Cross Disciplinary Team Lead, DO2
Yufan (Frank) Liu, PharmD, Clinical Analyst, DO2
Yixuan Dong, PhD, Clinical Pharmacology Team Leader, Division of Cancer Pharmacology II (DCP II)
Dapeng Cui, PhD, Clinical Pharmacology Reviewer, DCP II
Flora Mulkey, MS Biostatistical Team Leader, Division of Biometrics V (DBV)
Michelle Marcovitz, PhD, Biostatistical Reviewer, DBV
Idara Ojofeitimi, MS, Chief, Project Management Staff, Division of Regulatory Operations (DRO)
Ashley Lane, MS, Senior Regulatory Health Project Manager, Division of Regulatory Operations (DRO)

SPONSOR ATTENDEES
Erik Anderson, MD, PhD, Executive Director, Global Development
I-Fen Chang, PharmD, Vice President, Global Development
Wenny Du, MS, MBA, Senior Director, Global Regulatory Affairs
Michelle Garcia, MSN, CPNP, Senior Manager, Global Regulatory Affairs
Ali Hamidi, MD, Medical Director, Global Patient Safety
Tony Jiang, PhD, Director, Biostatistics
Hannah Kim, PharmD, Manager, Global Regulatory Affairs
Jackie Kline, PhD, Vice President, Global Regulatory Affairs
Mukul Minocha, PhD, Director, Clinical Pharmacology Modeling & Simulation
Diana Gauto, MD, Medical Director, Global Development
Mohamed Shabooti, MD, Executive Medical Director, Global Patient Safety
Ramachandran Suresh, PhD, Associate Vice President, Biostatistics

BACKGROUND

Meeting Purpose

On March 21, 2025, Amgen Inc. (Amgen) submitted a Type B, Pre-sBLA meeting request to obtain feedback and agreement that the Study 20210004 data provide an adequate basis for submission of a supplemental BLA (sBLA) and will support conversion to traditional approval for BLA 761344 [redacted] (b) (4) [redacted].

FDA sent Preliminary Comments to Amgen on May 12, 2025.

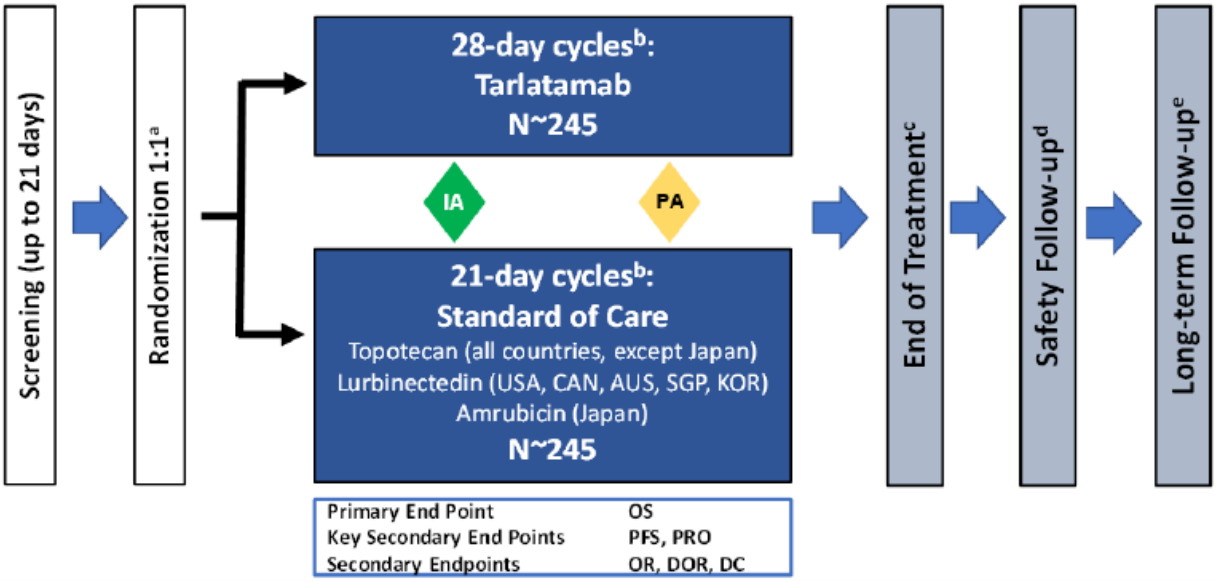
Regulatory

On May 16, 2024, FDA granted accelerated approval to tarlatamab for the treatment of patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy. Approval was based on results from 99 patients with relapsed/refractory ES-SCLC (with disease progression on platinum-based chemotherapy and one other systemic therapy) treated with tarlatamab at an initial dose of 1 mg on Cycle 1 Day 1 followed by 10 mg on Cycle 1 Day 8 and Day 15 then every 2 weeks thereafter. Overall response rate (ORR) was 40% (95% CI: 31, 51) and median duration of response (DOR) was 9.7 months (range 2.7, 20.7+).

On July 16, 2024, FDA received a Type C meeting request from Amgen to obtain feedback on the structure, content, and format aspects of a planned sBLA. Additionally, Amgen was seeking feedback on the proposed principal concepts for the integrated summary of safety and the integrated summary of efficacy. On September 24, 2024, a Written Response was issued addressing each of these items.

Clinical

Amgen proposes to submit an sBLA based on the results of Study 20210004, an open-label, randomized trial of tarlatamab compared to investigator's choice standard of care (SoC) in patients with ES-SCLC with disease progression on or after first-line platinum-based chemotherapy. The primary efficacy endpoint is overall survival (OS), with progression-free survival (PFS) by investigator assessment and patient reported outcomes (PRO) as key secondary endpoints. A figure of the study schema is provided below. This trial is intended to verify the clinical benefit of tarlatamab which is currently under accelerated approval.



Source: Figure 3 of meeting materials

A total of 509 patients were randomized, with 255 patients randomized to the SoC arm and 254 to the tarlatamab arm. Of the 255 patients randomized to the SoC arm, 244 received treatment with 176 receiving topotecan, 45 receiving lurbinectedin and 23 receiving amrubicin. Of the 254 patients randomized to the tarlatamab arm, 252 received tarlatamab. Baseline demographic and disease characteristics were generally balanced across treatment arms.

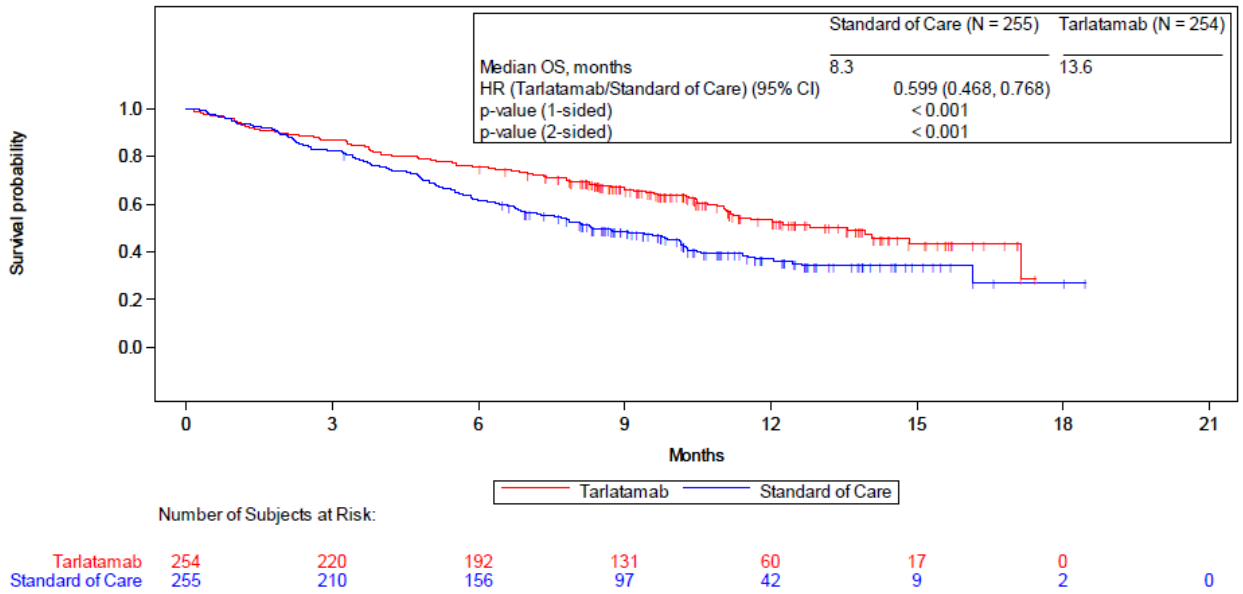
Table 1. Baseline Demographics and Disease Characteristics in the intention-to-treat (ITT) population

Demographic		Tarlatamab (n=254) %	Standard of Care (n=255) %
Sex	Male	72	66
Age	Median (min, max)	64 (20 – 86)	66 (26 – 84)
	< 65 years	51	45
	≥ 65 years	49	55
	≥ 75 years	12	10
Race	White	60	55
	Black/African American	0.8	1.2
	Asian	38	42
	Other	0.4	1.2
Ethnicity	Hispanic/Latino	4.7	4.3
Region	Europe	50	44
	Asia	38	43
	North America	5	6
	Rest of World	7	7
ECOG Performance Status	0	33	31
	1	67	68
Smoking Status	Never	9	12
	Current	21	20
	Former	70	68
Prior Lines of Therapy	1	98	97
	≥2	2	3
Prior PD-(L)1 Therapy	Yes	71	71
Chemotherapy-free Interval	<90 days	43	45
	≥90 days	57	55
DLL3 Cut-offs	<75% at 2+ and 3+ staining intensity	47	45
	≥75% at 2+ and 3+ staining intensity	39	39
	<25% at 2+ and 3+ staining intensity	21	20
	≥25% at 2+ and 3+ staining intensity	65	64

Source: Table 14-2.1.1 and Table 14-2.2.1 of Meeting Package Appendix

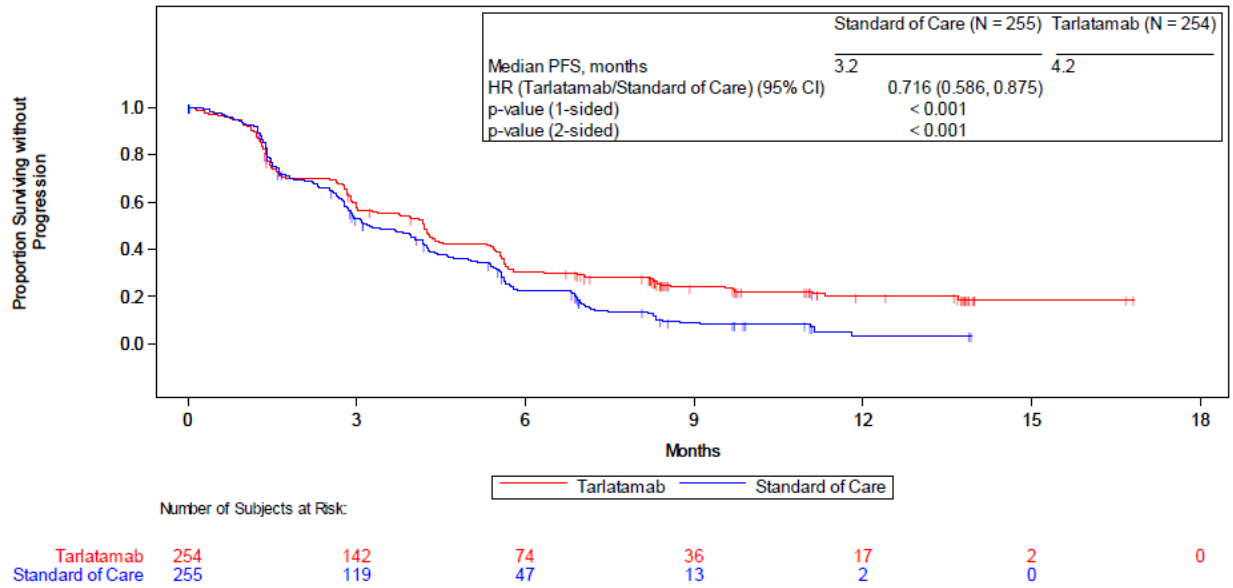
Per protocol specified criteria, an interim analysis was triggered with a data cutoff date of January 29, 2025. At the interim analysis, there were 263 deaths across the two arms (approximately 76% information fraction). Tarlatamab demonstrated a statistically significant improvement when compared to SoC for the primary endpoint of OS, with median OS 13.6 months vs 8.3 months (stratified hazard ratio [HR] = 0.599 [95% CI: 0.468, 0.768], p-value <0.001). A statistically significant improvement was also observed for the key secondary endpoint of PFS (median PFS 4.2 months vs 3.2 months, HR = 0.716 [95% CI: 0.586, 0.875], p-value <0.001). Kaplan-Meier plots of the OS and PFS results are provided below.

Figure 1. Kaplan-Meier plot of Overall Survival Results



Source: Figure 4 of Meeting Package

Figure 2. Kaplan-Meier plot of PFS Results



Source: Figure 5 of Meeting Package

Although not formally tested, tarlatamab demonstrated a higher ORR of 35% (95% CI: 29, 41) with a median DOR of 6.9 months (95% CI: 4.5, 12) vs. SoC ORR of 20% (95% CI: 16, 26) with a median DOR of 5.5 months (95% CI: 4.2, 6).

A summary of safety for study 20210004 are presented in the Table below.

Table 2. Summary of Safety Results for Study 20210004

	Tarlatamab (n=252)	Standard of Care (n=244)
≥Grade 3 TEAEs	54%	80%
Serious TEAEs	51%	51%
Fatal TEAEs	8%	9%
TEAEs leading to treatment discontinuation	5%	12%
TEAEs leading to dose interruption or reduction	37%	65%

Source: Table 14-6.1.1 of Meeting Package Appendix

The most common treatment emergent adverse events (TEAEs) (occurring in ≥20% patients in either tarlatamab or SoC were anemia (31% vs 64%), fatigue (29% vs 30%), cytokine release syndrome (CRS) (56% vs 1.2%), decreased appetite (35% vs 22%), nausea (24% vs 32%), constipation (29% vs 22%), neutropenia (11% vs 31%), pyrexia (27% vs 11%), leukopenia (10% vs 22%), thrombocytopenia (6% vs 25%) and dysgeusia (24% vs 1.6%).

Of the patients who experienced CRS, only three (1.2%) patients had Grade 3 CRS and no patients had grade 4 or 5 CRS. Overall, 43 patients were enrolled under the 6- to 8-hour monitoring criteria and 209 patients enrolled under the 48-hour monitoring criteria. No patients under the tarlatamab 6- to 8-hour monitoring and three (1.4%) patients

under the 48-hour monitoring criteria had Grade ≥3 CRS events during the first two doses. Using an Amgen MedDRA query for immune effector cell-associated neurotoxicity syndrome (ICANS), 21 (8%) patients experienced a TEAE of ICANS with 1 patient having an event that was Grade ≥3; this was a fatal event.

sBLA Proposal

Based on the interim analysis results, Amgen intends to submit an sBLA in June 2025. Amgen has requested participation in Project Orbis and the Real Time Oncology Review (RTOR) program along with priority review. A list of the studies Amgen intends to include in the sBLA are provided in the table below.

Study number	Study Population/Design
20210004 (monotherapy) N=509	Open-label randomized study of tarlatamab vs. standard of care in patients with SCLC after 1st line platinum-based chemotherapy.
20200491 (monotherapy) N=222	Dose randomized study in patients with relapsed/refractory SCLC after two or more prior lines of treatment including 1 platinum-based regimen
20160323 (monotherapy) N=270	First-in-human dose escalation and expansion study of relapsed/refractory SCLC patients who progressed or recurred following at least 1 platinum-based regimen
20230016 (monotherapy) N=181	Tarlatamab vs. placebo in patients with LS-SCLC who have not progressed following concurrent chemoradiation therapy (Limited stage maintenance therapy setting)
20200041 (in combination with durvalumab) N=362	Durvalumab + tarlatamab vs. durvalumab after treatment with etoposide/platinum and durvalumab (Maintenance therapy)
20230273 (monotherapy) N=32	Tarlatamab in Chinese patients with advanced SCLC after 2 or more prior lines of treatment

Source: Table 4 of Meeting Package

Amgen proposes to use pooled safety data from Studies 20200491 and 20160323 to further characterize the safety profile of tarlatamab. The data package will also include supportive blinded aggregate safety data from Studies 20230016 and 20200041 as well as CRS data from Study 20230273, as additional evidence supporting the safety profile of tarlatamab.

(b) (4)

(b) (4)

SPONSOR QUESTIONS AND FDA RESPONSES

Clinical Question

1. Does the Agency agree that the clinical data from Study 20210004 and the pooled safety data from studies of tarlatamab 10 mg monotherapy in SCLC (Studies 20210004, 20200491, 20160323) with supportive safety data from Studies 20230016, 20200041, 20230273 provide an adequate basis for submission of an sBLA intended to support conversion to traditional approval for BLA 761344 in the proposed indication?

FDA Response: We agree that the available data appear appropriate to support submission of an sBLA.

Amgen's Response Received via Email on May 14, 2025: Amgen acknowledges the Agency's comment.

Discussion During Meeting: Discussion did not occur during the meeting.

Safety Questions

2. (b) (4)

Amgen's Response Received via Email on May 14, 2025: Amgen acknowledges the Agency's comment.

Discussion During Meeting: Discussion did not occur during the meeting.

3. (b) (4)

(b) (4). As this study was not discussed during the content and format meeting, please confirm that this study will also be included/updated as part of the 90-day safety update.

Amgen's Response Received via Email on May 14, 2025: The last subject in Study 20230273 was enrolled on 09 January 2025 with a data cutoff date of 28 March 2025 for the primary analysis. This cutoff date is proximate to the 90-day cutoffs for Studies 20160323, 20200491, and 20210004. Given the timing of the Study 20230273 data cutoff and the maturity of the CRS data, i.e., all subjects have completed Cycle 1 and thus expected CRS events would have already occured, Amgen is able to provide comprehensive CRS analysis as standalone tables in the sBLA.

Amgen will include the CRS analysis from Study 20230273 as standalone tables, separate from the ISS, in Module 5.3.5.3 of the sBLA submission to support the evaluation of cytokine release syndrome. This CRS analysis will not be pooled within the ISS. The Study 20230273 clinical study report will not be included in the sBLA, nor will the efficacy, safety, and PK data sets from this study.

As no further enrollment, data cuts, or analyses are planned for Study 20230273 beyond the primary analysis, no additional data from this study will be included in the 90-day safety update.

Amgen's Response Received via Email on May 15, 2025: Following further internal review of our safety data and with the goal of expediting patient access to tarlatamab, we would like to respectfully request the opportunity to discuss the feasibility of waiving the 90-day safety update requirement during our upcoming meeting. We recognize that this topic was not included in our original meeting request or briefing package and that we have already submitted responses to FDA's preliminary comments. However, given the timing and potential impact on the review timeline, we believe it would be valuable to seek FDA's perspective on this matter during the scheduled discussion.

For Study 20210004, the DCO for the sBLA submission was 01/29/25. At this initial DCO there were 509 subjects enrolled, of which 496 were dosed and evaluable for safety, with 245 subjects remaining on study and 88 on treatment. The DCO for the 90-day update was 04/29/25 with an estimated 200 subjects remaining on study and 70 on treatment. The 90-day update would provide an incremental safety update and include approximately 40% of the total study population. Based on the known time to onset of CRS, we do not anticipate that this additional data would meaningfully impact the safety conclusions presented in the sBLA submission.

Discussion During Meeting: FDA did not agree to Amgen's request to waive the 90-day safety update. FDA acknowledged Amgen's rationale that additional

data may not provide additional information regarding CRS toxicity but stated that, given the relatively limited safety data available for tarlatamab and other associated risks outside of CRS toxicity, additional safety data should be provided in the 90-day safety update.

Amgen stated that for Study 20230273 (Delphi-307), Amgen planned to submit only data on CRS toxicity in the sBLA submission. FDA stated that given this, along with the fact that Delphi-307 is a small, single arm trial, Amgen's proposal to not include any updated information from Delphi-307 in the 90-day safety update is acceptable.

Data Collection Question

4. During Study 20210004, no data for the U.S. conventional unit was collected for lab results. Therefore, Amgen plans to only provide International System of Units (SI) in LBSTRESU for the SI results in the LBSTRESC and LBSTRESN fields. Does the Agency agree?

FDA Response: No, we do not agree. We recommend that you convert the lab results so that both conventional units and SI units are provided in the submission package.

Amgen's Response Received via Email on May 14, 2025: Amgen acknowledges the Agency's comment and will provide both conventional units and SI units in the submission package.

Discussion During Meeting: Discussion did not occur during the meeting.

Regulatory Questions

5. Does the Agency agree that the clinical safety and efficacy data from the phase 3 Study 20210004 and the supporting studies provide an adequate basis for Priority Review?

FDA Response: The determination of review designation is made after submission of the sBLA.

Amgen's Response Received via Email on May 14, 2025: Amgen acknowledges the Agency's comment.

Discussion During Meeting: Discussion did not occur during the meeting.

6. Real Time Oncology Review and Project Orbis

a. Does the Agency agree that the planned sBLA qualifies for participation in the Real Time Oncology Review (RTOR) program? If yes, does the Agency agree with the proposed content and timelines for the pre-submission batches?

FDA Response: We agree that the planned sBLA is appropriate for participation in the RTOR program. We have no objections to the proposed content and timelines for the pre-submission batches.

Amgen's Response Received via Email on May 14, 2025: Amgen acknowledges the Agency's comment.

Discussion During Meeting: Discussion did not occur during the meeting.

b. Given the top-line results from the pivotal phase 3 Study 20210004, can the Agency advise if the planned sBLA could be selected for Project Orbis? In the event that the application is selected, can the Agency advise on the timing of communicating its decision to Amgen and the countries they would consider for Project Orbis?

FDA Response: We agree that the planned sBLA is appropriate for participation in Project Orbis.

Please submit a Project Orbis Request for Participation and Global Submission Plan. The submission forms can be found on the Project Orbis website, available at: https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis. We will communicate the countries that would participate in Project Orbis in approximately one month after receipt of the global submission plan.

Once the supplement number has been assigned, please send the Sponsor Authorization Letters for the participating Project Orbis Partners.

Amgen's Response Received via Email on May 14, 2025: Amgen acknowledges the Agency's comment and plans to submit the Project Orbis Request for Participation and Global Submission Plan in the near term.

Discussion During Meeting: Discussion did not occur during the meeting.

ADDITIONAL FDA COMMENTS

Clinical

7. We note that there were 11 patients in the SoC arm and 2 patients in the tarlatamab arm who were randomized but did not receive treatment. In your submission, please provide the reason these patients did not receive treatment and/or dropped out of the study.

Amgen's Response Received via Email on May 14, 2025: Amgen acknowledges the Agency's comment and will provide this information in the Study 20210004 CSR.

Discussion During Meeting: Discussion did not occur during the meeting.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric

Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance

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[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

with the format items in regulations and guidances.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

BIORESEARCH MONITORING INSPECTION PLANNING

Submit the data and information described in the guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* in your application. [6] The data and information will be used to plan BIMO inspections, facilitate the timely identification of sites for inspection, and ensure that field investigators from the Agency have the information needed to conduct the inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). The guidance should be used in conjunction with the *Bioresearch Monitoring Technical Conformance Guide*, or BIMO TCG, when preparing the required data and information.[7] The BIMO TCG provides more specific directions related to formatting and is updated routinely to provide current specifications, recommendations, and general considerations for preparing the data and information.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs,

[6] https://www.fda.gov/media/85056/download
[7] https://www.fda.gov/media/85061/download

including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR.[8] In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[9]

REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[10] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

[8] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[9] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project
[10] https://www.fda.gov/media/124795/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ASHLEY R LANE
05/16/2025 04:34:06 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761344Orig1s001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From: Lane, Ashley
Sent: Tue 18 Nov 2025 11:12:52 AM -0500 UTC
To: Garcia, Michelle
Subject: [FDA Information Request: Draft USPI & MG] BLA 761344-S001/Amgen/tarlatamab/Round 5 [USPI]/Round 2 [MG]
Attachments: Draft PI_tarlatamab_BLA 761344-S001_To Amgen 11.18.2025_Round 5_TC.docx, Draft MG_tarlatamab_BLA 761344-S001_To Amgen 11.18.2025_Round 2_TC.docx, Draft PI_tarlatamab_BLA 761344-S001_To Amgen 11.18.2025_Round 5_TC.pdf, Draft MG_tarlatamab_BLA 761344-S001_To Amgen 11.18.2025_Round 2_TC.pdf
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025.

Please find attached FDA's proposed edits containing comments (in PDF and Word versions) to your draft USPI and Medication Guide.

In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Amgen" in the comment field) stating your agreement.

For those edits which you do not agree, provide a comment (cite "From Amgen" in the comment field) and include justification for your counterproposal.

If Amgen agrees with FDA's proposed changes, please submit the finalized draft versions of the USPI and Medication Guide as soon as possible by no later than today, **Tuesday, November 18, 2025, 3:00 PM EST**. In addition to submitting your formal response to BLA 761344, please email me a copy of your response as well as a clean and redlined version of the labeling.

Please acknowledge receipt of this email and the attachments.

Regards,

Ashley R. Lane, MS
Senior Regulatory Health Project Manager
U.S. Food and Drug Administration
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ASHLEY R LANE
11/18/2025 12:20:27 PM

From: Lane, Ashley
Sent: Fri 14 Nov 2025 05:32:40 PM -0500 UTC
To: 'Garcia, Michelle'
Subject: [FDA Information Request: Draft USPI] BLA 761344-S001/Amgen/tarlatamab/Round 4-USPI/Round 1-MG
Attachments: Draft MG_tarlatamab_BLA 761344-S001_To Amgen 11.14.2025_Round 1_TC.docx, Draft PI_tarlatamab_BLA 761344-S001_To Amgen 11.14.2025_Round 4_TC.pdf, Draft MG_tarlatamab_BLA 761344-S001_To Amgen 11.14.2025_Round 1_TC.pdf, Draft PI_tarlatamab_BLA 761344-S001_To Amgen 11.14.2025_Round 4_TC.docx
Importance: High

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A response to FDA's proposed changes is requested as soon as possible by no later than **Monday, November 17, 2025, COB, EST**. In addition to submitting your formal response to BLA 761344, please email me a copy of your response as well as a clean and redlined version of the labeling.

Please acknowledge receipt of this email and the attachments.

Regards,

Ashley R. Lane, MS
Senior Regulatory Health Project Manager
U.S. Food and Drug Administration
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
11/14/2025 05:35:14 PM

From: Lane, Ashley
Sent: Wed 05 Nov 2025 02:32:31 PM -0500 UTC
To: Arredondo Pimentel, Claudia
Cc: Garcia, Michelle
Subject: FW: [FDA Information Request: Draft USPI] BLA 761344-S001/Amgen/tarlatamab/Round 3
Attachments: Draft PI_tarlatamab_BLA 761344-S001_To Amgen 11.5.2025_TC.docx, Draft PI_tarlatamab_BLA 761344-S001_To Amgen 11.5.2025_TC.pdf
Importance: High

Dear Claudia,

I received an out of office message from Michelle when I sent the USPI for Round 3 of labeling negotiations. Would you mind forwarding to her coverage?

Thank you!

Take care,
Ashley

Ashley R. Lane, MS
Senior Regulatory Health Project Manager
U.S. Food and Drug Administration
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

From: Lane, Ashley
Sent: Wednesday, November 5, 2025 2:24 PM
To: 'Garcia, Michelle' <mgarci09@amgen.com>
Subject: [FDA Information Request: Draft USPI] BLA 761344-S001/Amgen/tarlatamab/Round 3
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025.

Please find attached FDA's proposed edits containing comments (in PDF and Word versions) to your draft USPI.

In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Amgen" in the comment field) stating your agreement.

For those edits which you do not agree, provide a comment (cite "From Amgen" in the comment field) and include justification for your counterproposal.

A response to FDA's proposed changes is requested by **Friday, November 7, 2025, COB, EST**. In addition to submitting your formal response to BLA 761344, please email me a copy of your response as well as a clean and redlined version of the labeling.

Please acknowledge receipt of this email and the attachments.

Regards,

Ashley R. Lane, MS
Senior Regulatory Health Project Manager
U.S. Food and Drug Administration
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
11/05/2025 02:52:41 PM

From: Lane, Ashley
Sent: Wed 29 Oct 2025 07:36:13 PM -0400 UTC
To: Garcia, Michelle
Subject: [FDA Information Request: Draft USPI] BLA 761344-S001/Amgen/tarlatamab/Round 2
Attachments: Draft PI_tarlatamab_BLA 761344-S001_To Amgen 10.29.2025_TC.docx, Draft PI_tarlatamab_BLA 761344-S001_To Amgen 10.29.2025_TC.pdf
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025.

Please find attached FDA's proposed edits containing comments (in PDF and Word versions) to your draft USPI.

In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Amgen" in the comment field) stating your agreement.

For those edits which you do not agree, provide a comment (cite "From Amgen" in the comment field) and include justification for your counterproposal.

A response to FDA's proposed changes is requested by **Friday, October 31, 2025, 4:00 PM EDT**. In addition to submitting your formal response to BLA 761344, please email me a copy of your response as well as a clean and redlined version of the labeling.

Please acknowledge receipt of this email and the attachments.

Regards,

Ashley R. Lane, MS
Senior Regulatory Health Project Manager
U.S. Food and Drug Administration
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
10/29/2025 07:39:54 PM

From: Lane, Ashley
Sent: Fri 17 Oct 2025 05:24:36 PM -0400 UTC
To: mgarci09@amgen.com
Subject: [FDA Information Request: Draft USPI] BLA 761344-S001/Amgen/tarlatamab/Round 1
Attachments: Draft PI_tarlatamab_BLA 761344-S001_To Amgen 10.17.2025_TC.docx, Draft PI_tarlatamab_BLA 761344-S001_To Amgen 10.17.2025_TC.pdf
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025.

Please find attached FDA's proposed edits containing comments (in PDF and Word versions) to your draft USPI.

In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Amgen" in the comment field) stating your agreement.

For those edits which you do not agree, provide a comment (cite "From Amgen" in the comment field) and include justification for your counterproposal.

A response to FDA's proposed changes is requested by **Wednesday, October 22, 2025, 12:00 PM EDT**. In addition to submitting your formal response to BLA 761344, please email me a copy of your response as well as a clean and redlined version of the labeling.

Please acknowledge receipt of this email and the attachments.

Regards,

Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

strictly prohibited. If you think you have received this email message in error, please email the sender immediately at Ashley.Lane@fda.hhs.gov.

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/s/

ASHLEY R LANE
10/17/2025 05:28:35 PM

From: Lane, Ashley
Sent: Tue 14 Oct 2025 12:43:38 PM -0400 UTC
To: 'mgarci09@amgen.com'
Subject: BLA 761344/S-001: Clinical Comments--Response Required (Due: 10/20/2025)
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025. The clinical reviewer for this sBLA has the following comments:

1. We note fatal cases of CRS from your PBRERs for tarlatamab. Please provide narratives for all fatal cases of CRS in the postmarketing setting to date.

2. We are not able to verify the number of patients with dose interruptions from the DeLLphi-304 dataset (we have 95 patients and you have 96 patients from your 90 day safety update table) for tarlatamab. For your ADAE dataset, we utilized the following flags: TRTEMFL=Y, SAFFL=Y, AEACN=drug interrupted. We also note that there is one patient (b) (6) who has AEACN=dose reduced. Please verify if this patient had their dose reduced and confirm whether our logic for dose interruptions is correct.

3. Please provide the following details from patients who died due to an AE:

    a. The narratives for patients (b) (6) state the patient died due to disease progression. Please provide the dates of progression in relation to the date of death and last dose of tarlatamab and any further details surrounding the patient's death that would provide support that the death was due to disease progression (e.g., symptoms around death, details surrounding target lesions, non target lesions, which lesions had progressed and the degree of tumor burden increase).

    b. For the narrative of patient (b) (6) the investigator concluded this was more likely due to a cardiovascular event such as a stroke instead of ICANS. Please provide details on how the investigator came to this conclusion.

    c. The narrative of patient (b) (6) states that the patient had imaging revealed to be of thoracic infectious pathology. Please provide further details on how the investigator reached this conclusion that this was of infectious etiology.

Please provide a response to the above comments, as requested, by **Monday, October 20, 2025, COB, EDT**, via email to me, followed by a formal submission to the BLA. If you have any questions, please contact me via email. Also, please respond to confirm receipt of this communication.

Regards,

Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
10/14/2025 12:49:31 PM

From: Lane, Ashley
Sent: Tue 14 Oct 2025 11:25:52 AM -0400 UTC
To: 'mgarci09@amgen.com'
Subject: BLA 761344/S-001: Clinical Comments--Response Required (Due: 10/15/2025)
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025. The clinical reviewer for this sBLA has the following comments:

1. For Section 5 of the proposed label, we have modified the ranges for median time to onset of all grade CRS and grade >=2 CRS to reflect the min, max of the table and not the Q1, Q3 variable per Table T14-6.6.1 of the ISS. However, we note that the bottom end of the range includes an onset of 0 hours which does not appear plausible to us unless the event occurred right at the immediate start of infusion. Please explain the logic in deriving the range and verify/update your number as appropriate.

2. For Section 5.3 of the proposed label, we note that an AMQ was used in deriving the percentage for neutropenia. However, it is not clear to us how the numbers were derived for decreased platelets and decreased hemoglobin. Please explain this.

3. For Section 5.4 of the proposed label, our numbers slightly differ from yours in the 90DSU. We utilized the 90 DSU ISS ADAE dataset with the following flags: TRTEMFL=Y, SAFFL=Y, TRT01A=AMG757 10 mg. From these, we have 202 patients and 65 patients with Grade 3+ events from the infection and infestations SoC which differ from your numbers in the ISS slightly. Please review our logic.

4. We were not able to verify your lab abnormality numbers in Section 6 of the label. For the ADLB dataset we used the following logic. ABLFL=Y and PSBFL=Y to define the number of evaluable patients per lab analyte. ATOXICHG =1, 2, 3 or 4 to determine number of patients with increase shift from baseline and ATOXDCHG=1, 2, 3 or 4 to determine the number of patients with decrease shift from baseline. In addition, we could not use this logic for specific labs such as liver enzyme values as ATOXICHG and ATOXDCHG are not populated for these; we ask that you explain your logic in deriving the abnormalities for these labs as well which will also be important for Section 5 of the label.

5. For Section 6 of the label, the demographics should be of the safety population and not the ITT population. We could not locate a table for this in the DeLLphi-304 CSR. Please provide these numbers.

6. Your previous response regarding differences in vital sign abnormalities across the 2 arms in DeLLphi-304 is not fully accepted. While we acknowledge there are differences in measuring vital signs, please provide an analysis showing whether these changes in

heart rate, respiratory rate, blood pressure were transient, whether there were any concurrent events explaining these changes and whether there were any new medications started in response to these findings.

Please provide a response to the above comments, as requested, by **Wednesday, October 15, 2025, COB, EDT**, via email to me, followed by a formal submission to the BLA. If you have any questions, please contact me via email. Also, please respond to confirm receipt of this communication.

Regards,

Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
10/14/2025 12:47:27 PM

From: Lane, Ashley
Sent: Mon 06 Oct 2025 04:54:46 PM -0400 UTC
To: 'mgarci09@amgen.com'
Subject: BLA 761344/S-001: Clinical Comments--Response Required (Due: 10/9/2025)
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025. The clinical reviewer for this sBLA has the following comments:

1. Please produce Table 14-6.11.3 of the ISS for all tarlatamab doses (including Cycle 1 Day 15, Cycle 2 onward; all grades together)

2. Please also produce Table 14-6.11.3 (all grades together, grade 1 and grade 2 separate) with the "Time from last prior tarlatamab administration to start of first event after each dose" fields ordered in the same way as Table 14-6.11.1 (e.g., >=0 to <=8, >8 to <=12, >12 to <=24, >24 to <=48 and >48).

3. Please reproduce Table 14-6.6.1 for CRS but break this out by monitoring period (24–48-hour monitoring [n=400], 6 to 8 hour monitoring [n=73] and overall [n=473]).

Please provide a response to the above comments, as requested, by **Thursday, October 9, 2025, COB, EDT**, via email to me, followed by a formal submission to the BLA. If you have any questions, please contact me via email. Also, please respond to confirm receipt of this communication.

Regards,

Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
10/06/2025 05:04:43 PM

U.S. FOOD & DRUG ADMINISTRATION

Ralph A. Mazenko, Associate Vice President of R&D Quality
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1730

Dear Mr. Mazenko:

This letter informs you of findings observed during the U.S. Food and Drug Administration (FDA) inspection conducted at Amgen, Inc. between August 4, 2025, and August 7, 2025. Investigator Lan T. Tran, representing FDA, reviewed your conduct as the sponsor of a clinical investigation (Protocol DeLLphi-304 (20210004), "A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared with Standard of Care in Subjects with Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy") of the investigational drug IMDELLTRA® (tarlatamab-dlle).

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects have been protected.

From our review of the FDA Establishment Inspection Report and the documents submitted with that report, we did not observe any violations of the applicable statutory requirements or FDA regulations that justify compliance or enforcement action.

No response to this letter is necessary. Should you have any questions, please write to me at the address below.

Sincerely,

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D., F.A.A.P.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5370
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

LORETO CORAZON Y LIM
09/19/2025 01:00:21 PM
Signed for Jenn Sellers, M.D., Ph.D., F.A.A.P.

From: Estrada, Monica
Sent: Thu 11 Sep 2025 01:48:24 PM -0400 UTC
To: 'Garcia, Michelle'
Cc: Lane, Ashley
Subject: BLA 761344/S-001: Additional Clinical Comment -- Response Required (Due 9/18/25)
Importance: High

Dear Michelle Garcia,

This communication is being sent on behalf of the RPM who manages this BLA, Ashley Lane.

FDA refers to your supplemental BLA submission, under BLA 761344/S-001, submitted and received on June 18, 2025. The clinical reviewer for this BLA has the following additional comment:

1. In Table 9-4 of the DeLLphi-304 CSR, the proportion of patients with Stage IV disease at screening is 92% while the proportion of patients with metastatic disease at baseline was 91%. Please explain this difference.

Please provide a response to the above comment, as requested, by **Thursday, September 18, 2025, EOB, EST**, via email to Ashley Lane, followed by a formal submission to the BLA.

Kindly confirm receipt of this communication.

Best Regards,
Monica

Monica Estrada
Project Coordinator
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research
Email: Monica.Estrada@fda.hhs.gov

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/s/

MONICA ESTRADA
09/11/2025 01:54:43 PM

From: Estrada, Monica
Sent: Wed 10 Sep 2025 07:55:25 PM -0400 UTC
To: mgarci09@amgen.com
Cc: Lane, Ashley
Subject: BLA 761344/S-001: Clinical Comment -- Response Required (Due 9/16/25)
Importance: High

Dear Michelle Garcia,

This communication is being sent on behalf of the RPM who manages this BLA, Ashley Lane.

FDA refers to your supplemental BLA submission, under BLA 761344/S-001, submitted and received on June 18, 2025. The clinical reviewer for this BLA has the following comments:

1. Your CSR narrative provided for patient (b) (6) appears incomplete. Please provide further details on the signs and symptoms the patient experienced, the treatments the patient received and any other relevant details. The other fatal narratives also appear to be autogenerated with very few details describing the course of each adverse event. Please resubmit all grade 5 tarlatamab narratives in this fashion. In addition, please provide a narrative for all other deaths that occurred while on-treatment.

2. Your protocol eligibility criteria require patients to have an ECOG PS of 0 or 1. There appear to be 4 patients who were enrolled under an ECOG PS 2 and we could not locate any protocol deviations reported for these patients regarding this. Please clarify this.

3. We acknowledge that you have summarized your CRS data based primarily on the first 2 doses of treatment as the vast majority of events occur during this time period. However, please update the following ISS tables with included data from all tarlatamab doses: Table 14-6.1.10, 14-6.9.400, 14-6.11.1, 14-6.12.2, 14-6.12.4, 14-6.13.1. In addition, please provide data from these tables with data from study 20200491 (separated out by 24 hour modified monitoring cohort, 48 hour monitoring and combined)

4. In table 14-6.11.1, the summary of time from first tarlatamab administration to first onset of event (days) variable/field and the summary of time from first tarlatamab administration to first onset of event (hours) appears discrepant to us. For example, the median time from the former field is 2 days while the median time for the latter field is 15 hours. The number of patients also appear to be different between the 2 variables. Please clarify this.

5. There also appears to be discrepant data between table 14-6.12.2 (Summary of Time From Onset of Treatment-emergent Grade 1 CRS Events (AMQ Narrow) to Treatment-emergent Grade 2 CRS Events (AMQ Narrow) During First Two Tarlatamab Doses…) and Table 14-6.12.4 (Summary of Time From Onset of Treatment-emergent Grade 1 CRS Events (AMQ Narrow) to Treatment-emergent Grade 2 or Higher CRS Events (AMQ Narrow) by Dose During First Two Tarlatamab Doses….). In theory, the second table should have a higher number of patients as this would encapsulate patients who have transitioned from Grade 1 to Grade 2+ CRS vs. just to

Grade 2 CRS. However, the former table shows that 5% of patients had an onset of Grade 1 CRS to Grade 2 CRS while the latter shows 4% of patients had an onset of Grade 1 CRS to Grade 2+ CRS. Please clarify this discrepancy.

6. [redacted] (b) (4)

Could you also let me know if you plan on submitting an updated label based on the 90-day safety update data?

Please provide a response to the above comments by **Tuesday, September 16, 2025, EOB, EST**, via email to me, followed by a formal submission to the BLA.

Kindly confirm receipt of this communication.

Regards,
Monica

Monica Estrada
Project Coordinator
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research
Email: Monica.Estrada@fda.hhs.gov

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/s/

MONICA ESTRADA
09/11/2025 01:53:21 PM

From: Estrada, Monica
Sent: Wed 10 Sep 2025 08:00:31 PM -0400 UTC
To: Garcia, Michelle
Cc: Lane, Ashley
Subject: BLA 761344/S-001: Clinical Pharmacology Comments -- Response Required (Due 9/12/25)
Importance: High

Dear Michelle Garcia,

This communication is being sent on behalf of the RPM who manages this BLA, Ashley Lane.

FDA refers to your supplemental BLA submission, under BLA 761344/S-001, submitted and received on June 18, 2025. The clinical pharmacology reviewer for this BLA has the following comments:

1. Provide the full report of the bioanalytical method validation and performance in study 20210004, including but not limited to method reproducibility and long-term stability data for method BAL-II/MOA/115 by (b) (4) and ICSH 20-079 by (b) (4).

2. For method ICSH 20-079, cross validation should also be assessed by measuring study samples (if available) that span the study sample concentration range (n≥30) with both methods, or in both laboratories, per M10 guidance.

3. For method ICSH 20-079, clarify how you calculated the method reproducibility. If incurred sample reanalysis was performed in 79 out of 527 of study samples, the rate is 15% not 9% as reported.

Please provide a response to the above comments by **Friday, September 12, 2025, EOB, EST**, via email to me, followed by a formal submission to the BLA.

Kindly confirm receipt of this communication.

Regards,
Monica

Monica Estrada
Project Coordinator
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research
Email: Monica.Estrada@fda.hhs.gov

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/s/

MONICA ESTRADA
09/11/2025 01:52:04 PM

From: Lane, Ashley
Sent: Fri 05 Sep 2025 05:16:59 PM -0400 UTC
To: 'mgarci09@amgen.com'
Subject: BLA 761344/S-001: Statistical Comment--Response Required (Due: 9/10/2025)
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025. The statistical reviewer for this sBLA has the following comment:

1. Please include updated efficacy data with your 90-day safety update submission. Additionally, provide a projected timeline for the final overall survival (OS) analysis in the DeLLphi-304 study.

Please provide a response to the above comment, as requested, by **Wednesday, September 10, 2025, COB, EDT**, via email to me, followed by a formal submission to the BLA. If you have any questions, please contact me via email. Also, please respond to confirm receipt of this communication.

Regards,

Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
09/05/2025 05:21:20 PM

From: Lane, Ashley
Sent: Thu 04 Sep 2025 11:28:36 PM -0400 UTC
To: mgarci09@amgen.com
Cc: Estrada, Monica
Subject: BLA 761344/S-001: Clinical Comments--Response Required (Due: 9/11/2025)
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025. We refer also to your original BLA dated and received October 12, 2023, which received accelerated approval on May 16, 2024. The clinical reviewer for this sBLA has the following comments:

1. We note from your subgroup analysis that patients from North America had an OS HR of 1.5 in the DeLLphi-304 trial. While we acknowledge the smaller numbers, but please provide baseline demographic and disease characteristics for these patients with a listing of patient IDs and any potential plausible explanation for the noted outlier result for this subgroup.

2. Table 9-1 of the DeLLphi-304 CSR states that 5.9% of patients discontinued IP due to an AE while Table 12-6 states 5.2% of patients discontinued IP due to AEs. Please explain this discrepancy.

3. We note from Table 9-4 of the DeLLphi-304 CSR that not all patients have Stage IV disease. Please provide the proportion of patients who did not have ES-SCLC randomized in your study.

4. Please provide the proportion of patients randomized to DeLLphi-304 that had no DLL3 staining and if enough patients, any relevant efficacy outcomes in these patients.

5. Please separate out Table 12-2 and Table 14-6.3.5 to display AEs by dose interruption and reduction separately for SoC (we acknowledge reductions for tarlatamab were not allowed per protocol).

6. In Section 9.1 of the DeLLphi-304 CSR states that 2 patients randomized to SoC had AEs prior to first dose which led to discontinuation of IP. Please provide the patient IDs along with the AEs the patients experienced.

Please provide a response to the above comments, as requested, by **Thursday, September 11, 2025, COB, EDT**, via email to myself and Monica Estrada (copied on this email), followed by a formal submission to the BLA. If you have any questions, please contact me via email. Also, please respond to confirm receipt of this communication.

Regards,

Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
09/04/2025 11:42:47 PM

From: Lane, Ashley
Sent: Thu 28 Aug 2025 02:55:37 PM -0400 UTC
To: mgarci09@amgen.com
Subject: BLA 761344/S-001: Statistical Comment--Response Required (Due: 9/10/2025)
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025. The statistical reviewer for this sBLA has the following comment:

1. Please clarify reasons for non-target response assessment of progressive disease at each of the timepoints below for the following patients:

SUBJID	TRT01P	VISITNUM	RSORRES (RSTESTCD =TRGRESP)	TRORRES (TRSCAT = 'NON-TARGET)	RSORRES (RSTESTCD =NTRGRESP)	RSORRES (RSTESTCD =OVRLRESP)
(b) (6)	SOC	7012	SD	3 NT lesions present	PD	PD
	Tarlatamab	7018	PR	4 NT lesions present 2 NT lesions absent	PD	PD
	SOC	7006	SD	3 NT lesions present	PD	PD
	SOC	7006	SD	4 NT lesions present	PD	PD
	Tarlatamab	7006	SD	2 NT lesions present	PD	PD
	Tarlatamab	7012	PR	1 NT lesion presents	PD	PD
	SOC	7006	PR	1 NT lesion presents	PD	PD
	Tarlatamab	7018	PR	2 NT lesions present	PD	PD
	Tarlatamab	7012	SD	1 NT lesion presents	PD	PD
	Tarlatamab	7006	SD	4 NT lesions present	PD	PD
	SOC	7030	PR	4 NT lesions present	PD	PD
	SOC	7006	PR	3 NT lesions present	PD	PD

Please provide a response to the above comment, as requested, by **Wednesday, September 10, 2025, COB, EDT**, via email to me, followed by a formal submission to the BLA. If you have any questions, please contact me via email. Also, please respond to confirm receipt of this communication.

Regards,

Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
08/28/2025 02:58:53 PM

From: Lane, Ashley
Sent: Wed 20 Aug 2025 05:16:31 PM -0400 UTC
To: 'mgarci09@amgen.com'
Subject: BLA 761344/S-001: Clinical Outcome Assessment Comments--Response Required (Due: 9/10/2025)
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025. As part of FDA's review of safety and efficacy, we are interested in evaluating patient experience data including aspects of clinical outcome assessments that were collected in DeLLphi-304 (20210004).

- Provide the following analyses, figures, and summary tabulations described in detail below through the Week 19 timepoint.
- Provide an executive summary of your clinical interpretation of the most critical PRO results to inform FDA's benefit-risk assessment.

While some of the requested information may already be included in your BLA submission, it may not be presented or collated as requested here. Please limit your responses to the analyses and outcomes requested. If you feel additional information is needed to provide context for the requested analyses, put this additional information into a separate document and reference as needed.

Refer to FDA's Guidance for Industry Technical Specifications Document: Submitting Patient-Reported Outcome (PRO) Data in Cancer Clinical Trials for examples on dataset, table, and figure formatting (https://www.fda.gov/media/173581/download).

1. **Provide the tables and figures below for the following:**
   a. *Evaluating clinical benefit:* Change from baseline to Week 19 for:
      - Dyspnea (composite score) [EORTC QLQ-C30 Item 8, EORTC QLQ-LC13 Items 3, 4, 5]
      - Cough [EORTC QLQ-LC13 Item 1]
      - Chest Pain [EORTC QLQ-LC13 Item 10]
      - Physical Function Scale [EORTC QLQ-C30 Items 1-7, 20-27]

   b. *Informing safety and tolerability:* FACT-G GP5 and all PRO-CTCAE items

PRO Data Quality Information Request:

2. **Patient Disposition**

   a. Evaluating Clinical Benefit

Provide a table and figure documenting the cumulative patient disposition by arm per PRO assessment window (e.g., every 6 weeks) for all scheduled assessments. Use the following categories, if applicable:

- PRO expected
- PRO not expected due to death
- PRO not expected due to other reasons

See Example Table A4 and Figure A1 in FDA's PRO Technical Specification Guidance.

b. Informing the Evaluation of Safety and Tolerability

Provide a table and figure documenting the cumulative patient disposition by arm per PRO assessment window (e.g., every 6 weeks) for all scheduled assessments. Use the following categories, if applicable:

- PRO expected
- PRO not expected due to treatment discontinuation
- PRO not expected due to death
- PRO not expected due to other reasons

See Example Table A5 and Figure A2 in FDA's PRO Technical Specification Guidance.

3. **PRO Data Completeness**

a. Available Data Rate when Evaluating Clinical Benefit

Provide a table and figure documenting the PRO available data rates (denominator = randomized population) for each treatment arm at each assessment timepoint for each of the clinical benefit endpoints listed above.

The table should include reasons for missing observations by treatment arm and assessment. Reasons for missing observations include, but are not limited to, patient unable to complete due to disease progression, patient unable to complete due to adverse event, patient refusal, device failure, etc.

See Example Table A6 and Figure A3 in FDA's PRO Technical Specification Guidance.

b. Completion Rate for Safety and Tolerability

Provide a table and figure documenting the PRO completion rates (denominator = patients expected to complete the PRO measure at the designate PRO assessment time point) for each treatment arm, at each assessment for FACT-G GP5 and PRO-CTCAE.

The table should include reasons for missing observations among patients who were expected to complete the measure by treatment arm and assessment. Reasons for missing observations include, but are not limited to, patient refusal, patient unable to complete due to adverse event, device failure, etc.

See Example Table A7 and Figure A4 in FDA's PRO Technical Specification Guidance.

4. **Distributions**

a. Distribution of Categorical Responses

Provide a table and bar chart of the distribution of item-level responses for Cough and Chest Pain by arm per PRO assessment. Include number of patients who completed the PRO assessment, did not complete the PRO assessment, and were expected to complete the PRO assessment at each assessment for each arm.

See Example Table A8 and Figure A5 in FDA's PRO Technical Specification Guidance.

In addition, provide stacked bar charts for PRO-CTCAE items and FACT-G GP5 similar to the visualizations on FDA's Project Patient Voice accessible at: https://www.fda.gov/about-fda/oncology-center-excellence/project-patient-voice

b. Distribution of Change in Response Categories from Baseline (Evaluating Clinical Benefit)

Provide a table and bar chart for the item-level change in response categories from baseline for Cough and Chest Pain by arm per PRO assessment. Include number of patients who completed the PRO assessment, did not complete the PRO assessment, and were expected to complete the PRO assessment at each assessment for each arm below the bar chart.

See Example Table A10 and Figure A7 in FDA's PRO Technical Specification Guidance.

c. Summary statistics with Continuous Response Options (Evaluating Clinical Benefit)

Provide a table of summary statistics and line graph showing the descriptive means for Dyspnea (Composite) and the physical functioning subscale of the EORTC QLQ-C30 by arm per PRO assessment. Include number of patients who completed the PRO assessment, did not complete the PRO assessment, and were expected to complete the PRO assessment at each assessment for each arm below the line graph.

See Example Table A9 and Figure A6 in FDA's PRO Technical Specification Guidance.

d. Change from Baseline in Continuous Response Options when Evaluating Clinical Benefit

Provide a table and line graph showing LS means by arm per PRO assessment for change from baseline on Dyspnea (Composite) and change from baseline in EORTC QLQ-C30 Physical Function scale. The analysis population should include all randomized patients. Include number of patients who completed the PRO assessment and number of patients who did not complete the PRO assessment at each assessment for each arm below the line graph.

See Example Table A11 and Figure A8 in FDA's PRO Technical Specification Guidance but ensure that the analysis population is all randomized patients.

5. Review section 3.2.2.2 of the FDA's PRO technical Specification Guidance for details on how to represent missing data in the ADQS dataset. For each of the PRO-based endpoints included in the formal testing plan, re-submit a dataset that adheres to the guidance such that there is a row for each item score and summary score for all randomized patients at each planned (per protocol) PRO assessment timepoint, regardless of whether the item score or summary score has a value populated.

6. We are concerned about the interpretability of the PRO-based endpoints evaluating clinical benefit due to differential proportions of mortality between treatment arms at Week 19. We acknowledge that there is no best solution on how to address death as an intercurrent event. If the endpoint is driven by death, such that a large proportion of patients die by the time of the analysis, it severely impacts the estimated treatment effect and reduces its interpretability for clinical benefit. MMRM relies on the assumption that data are missing at random (MAR). If a patient is missing due to death, the MAR assumption is likely not a reasonable assumption, which leads to bias in the estimated treatment effect. Ultimately, results based on MMRM depends on the amount and reasons for missing data and how plausible the MAR assumption is for the study.

Reference is made to CSR 16.1.3.8: Patient Reported Outcomes (PRO) Secondary Analyses. Please clarify the following:

7. There is a discrepancy in the number of eligible subjects expected to complete PRO assessments at Weeks 7 and 13 in Table 8 of Section 7.1.1. Specifically, the expected number of subjects for Cough or Chest pain assessments (based on QLQ-LC13) differs from the expected number for Physical functioning assessments (based on QLQ-C30). Provide clarification on why the QLQ-C30 form was not expected to be completed by a subset of patients when the QLQ-LC13 form was expected for these weeks.

8. According to Table 12 of Section 7.1.3, only 88 patients in the SOC arm and 116 patients in the Tarlatamab arm completed the Week 19 PRO assessment. Whether the results

observed at Week 19 is representative for the whole population depends on how different the analysis set is to the ITT population. Provide a table that compares baseline demographics and disease characteristics for the following populations:

Tarlatamab Arm:

i. Patients who completed Week 19 PRO assessment (n=116)
ii. All patients randomized to receive tarlatamab (n = 254)

SOC Arm:

iii. Patients who completed Week 19 PRO assessment (n=88)
iv. All patients randomized to receive the SOC (n = 255)

9. Regarding sensitivity analyses by multiple imputation approach presented in Table 14 and 15 of Section 7.1.4, clarify if the imputed value was applied to all missing data, including those who were off the treatment, or only to those whose scores were expected. Describe detailed statistical analysis method and justify the imputation model specification used in the multiple imputation procedure.

While the above sensitivity analyses evaluating the robustness of results due to missing data are helpful, they still rely on strong untestable assumptions. Therefore, you should conduct the following additional sensitivity and supplementary analyses to explore the impact of death on the PRO-based endpoints:

10. Tipping point sensitivity analyses that systematically and comprehensively vary assumptions about the missing outcomes on the two treatment arms. The analyses should be two-dimensional, i.e., should allow assumptions about the missing outcomes on the two arms to vary independently, and should include scenarios where dropouts on drug tend to have worse outcomes than dropouts on control. Should also allow differential assumptions due to different reasons of dropouts.

11. An analysis incorporating PRO data collected from the follow-up safety period for patients who were not expected for PRO assessments due to study treatment discontinuation at week 7, 13 or 19.

Submit detailed statistical analysis plan for each of the analysis above, provide programs, justification of parameters used, and detailed results, as requested, by **Wednesday, September 10, 2025, COB, EDT**, via email to me, followed by a formal submission to the BLA. If you have any questions, please contact me via email. Also, please respond to confirm receipt of this communication.

Regards,

Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
08/20/2025 05:22:40 PM

BLA 761344/S-001

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Amgen Inc.
Attention: Michelle Garcia
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Michelle Garcia:

Please refer to your supplemental biologics license application (sBLA) received June 18, 2025, and your amendments, submitted under section 351(a) of the Public Health Service Act for Imdelltra (tarlatamab-dlle) injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is December 18, 2025.

We are reviewing your application according to the processes described in the draft guidance for industry *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications*.[1] Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any anticipated postmarketing requirements (PMRs) and postmarketing commitments (PMCs) by November 25, 2025.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

We request that you submit the following information:

Clinical

1. We note that approximately 5% of the randomized patients from DeLLphi-304 were from the U.S. We could not locate in your submission any document detailing the rationale for assuming the applicability of foreign data to the U.S. population. If this was not included in your original submission, please provide this.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[2] and Pregnancy and Lactation Labeling Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights of Prescribing Information and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
- Other prescription drug labeling resources for the Prescribing Information, patient labeling, and carton and container labeling.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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[2] Prescription Drug Labeling Resources website: https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[3] Pregnancy and Lactation Labeling Rule website: https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

NATIONAL DRUG CODE(s)

Prior to the action date of your sBLA, we recommend you:

- Review the regulations that describe the requirements for national drug code (NDC(s)) including the requirements for obtaining new NDC(s) and restrictions regarding the use of NDC(s) [see 21 CFR 207.33 and 21 CFR 207.35, respectively].

- Ensure that NDC(s) that appear on prescription drug labeling (e.g., Prescribing Information, outer packaging, carton labeling, container labeling) are assigned correctly per the above. CDER does not typically review the accuracy of NDC(s) on prescription drug labeling prior to approval.

- Optionally, reserve new NDC(s) by referring to the Drug Registration and Listing website[4] or contacting eDRLS@fda.hhs.gov. Include the required additional data elements when converting the NDC reservation submission to a drug registration and listing submission when a drug is approved.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed Prescribing Information (PI), Medication Guide (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

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[4] https://www.fda.gov/drugs/guidance-compliance-regulatory-information/electronic-drug-registration-and-listing-system-edrls

[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

Do not submit launch materials until you have received our proposed revisions to the Prescribing Information (PI), Medication Guide (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see FDA.gov.[6] If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, contact Ashley Lane, Senior Regulatory Health Project Manager, at Ashley.Lane@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Erin Larkins, M.D.
Director (Acting)
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

[6] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-prescription-drug-promotion-opdp

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/s/

ERIN A LARKINS
08/13/2025 12:02:10 PM

From: Lane, Ashley
Sent: Mon 21 Jul 2025 12:46:07 PM -0400 UTC
To: mgarci09@amgen.com
Subject: BLA 761344/S-001: Clinical Comment--Response Required (Due: 7/22/2025)
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025. We refer also to your original BLA dated and received October 12, 2023, which received accelerated approval on May 16, 2024. The clinical reviewer for this sBLA has the following comment:

1. Please provide the approximate date the 90-day safety update will be submitted.

Please provide a response to the above comment, as requested, by **Tuesday, July 22, 2025, COB, EDT**, via email to me, followed by a formal submission to the BLA. If you have any questions, please contact me via email. Also, please respond to confirm receipt of this communication.

Regards,

Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
07/21/2025 12:51:38 PM

From: Lane, Ashley
Sent: Tue 15 Jul 2025 11:06:00 AM -0400 UTC
To: mgarci09@amgen.com
Subject: BLA 761344/S-001: BIMO Comment--Response Required (Due: 8/20/2025)
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025. We refer also to your original BLA dated and received October 12, 2023, which received accelerated approval on May 16, 2024. The BIMO reviewer for this sBLA has the following comment:

1. During the review of Study 20200491 (DeLLphi-301) for the original biologics licensing application, FDA inspections conducted at clinical investigator Myung-Ju Ahn's site in Seoul, South Korea (Site #57002) observed a failure to conduct clinical studies in accordance with Good Clinical Practices. Specifically, 2 subjects did not meet eligibility criteria and there was underreporting of adverse events in 14 out of 19 patients enrolled at the site.

   Given the deficiencies identified from our FDA inspection for your original BLA, including a large number of underreported AEs, for Study 20210004 (DeLLphi-304), we request that you perform 100% SDR/SDV of subject eligibility and adverse events at the following sites and provide your findings: Site 73044 (PI Jing Zhang, Fuzhou, China), Site 58694 (PI Byoung Chul Cho, Seoul, South Korea) and Site 43756 (PI Yan Yu, Harbin, China), Site 34672 (PI Culeanin Tudor-Eliade, Cluj-Napoca, Romania), Site 63229 (PI Arslan Cagatay, Izmir, Turkey), and Site 65568 (PI Myung-Ju Ahn, Seoul, South Korea).

Please provide a response to the above comment, as requested, by **Wednesday, August 20, 2025, COB, EDT**, via email to me, followed by a formal submission to the BLA. If you have any questions, please contact me via email. Also, please respond to confirm receipt of this communication.

Regards,

Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
07/15/2025 11:10:09 AM

From: Lane, Ashley
Sent: Thu 10 Jul 2025 01:18:54 PM -0400 UTC
To: mgarci09@amgen.com
Subject: BLA 761344/S-001: Clinical Pharmacology Comments--Response Required (Due: 7/18/2025)
Importance: High

Dear Michelle,

FDA refers to your supplemental BLA (sBLA), under BLA 761344/S-001, submitted and received on June 18, 2025. The clinical pharmacology reviewer for this sBLA has the following comments:

1. Provide the identity of the reference used during cross-validation in method (b) (4) ICSH 20-079 as reported in Table 13 in the bioanalytical method validation Study 151089. Update Summary of Biopharmaceutic Studies and Associated Analytical Methods in Module 2.7.1 with method (b) (4) ICSH 20-079 that was used for study 20210004.

2. Clarify if all PK study samples were processed within 32 days at -60 to -80°C as this is covered by your current long term stability results. Otherwise, provide stability data that covers the longest storage duration If stability data does not cover the longest storage duration, then provide an updated PK analysis that omits PK samples that are not covered by the stability data.

Please provide a response to the above comments, as requested, by **Friday, July 18, 2025, COB, EDT**, via email to me, followed by a formal submission to the BLA. If you have any questions, please contact me via email. Also, please respond to confirm receipt of this communication.

Regards,

Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations, Office of New Drugs
Center for Drug Evaluation and Research

Email: Ashley.Lane@fda.hhs.gov
Phone: 301-796-9630

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/s/

ASHLEY R LANE
07/10/2025 01:24:16 PM

BLA 761344/S-001

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Amgen Inc.
Attention: Michelle Garcia
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Michelle Garcia:

We have received your supplemental biologics license application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA NUMBER: 761344

SUPPLEMENT NUMBER: 001

PRODUCT NAME: Imdelltra (tarlatamab-dlle) injection

DATE OF SUBMISSION: June 18, 2025

DATE OF RECEIPT: June 18, 2025

This supplemental application proposes to fulfill PMR 4635-1 and PMR 4635-2, and to convert the currently approved indication from accelerated approval to traditional approval based on efficacy results from Study 20210004, entitled "A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Subjects With Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy (DeLLphi-304)."

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **August 17, 2025**, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

RESPONSIBILITIES UNDER TITLE VIII OF FDAAA AND 42 CFR PART 11

You are also responsible for complying with the applicable provisions of section 402(j) of the Public Health Service Act (PHS Act) [42 U.S.C. § 282(j)], including its implementing regulations in 42 CFR part 11. Section 402(j) of the PHS Act was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Unless you have delegated your responsibilities to another entity, you are the "responsible party" and are required to submit registration and results information for each "applicable clinical trial" to the ClinicalTrials.gov data bank, as provided by section 402(j) of the PHS Act and 42 CFR part 11.

If you have any questions, please contact me via email at Ashley.Lane@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ashley Lane, MS
Senior Regulatory Health Project Manager
Office of Regulatory Operations
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

ASHLEY R LANE
06/24/2025 05:57:05 PM

IND 134859

MEETING MINUTES

Amgen Inc.
Attention: Michelle Garcia
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 27-2-D
Thousand Oaks, CA 91320

Dear Michelle Garcia:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMG 757.

We also refer to the meeting between representatives of your firm and the FDA on May 16, 2025. The purpose of the meeting was to obtain feedback and agreement that the Study 20210004 data provide an adequate basis for submission of a supplemental BLA and will support conversion to traditional approval for BLA 761344 (b) (4) .

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, please contact me via electronic mail at Ashley.Lane@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ashley Lane, MS
Senior Regulatory Health Project Manager
Office of Regulatory Operations
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes