

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761344Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

|                                                                           |                                                                                                                                                 |
|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| IND/NDA/BLA #                                                             | 134859                                                                                                                                          |
| Request Receipt Date                                                      | August 28, 2023                                                                                                                                 |
| Product                                                                   | Tarlatamab                                                                                                                                      |
| Indication                                                                | Treatment of adult patients with extensive stage small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy |
| Drug Class/Mechanism of Action                                            | Bispecific T-cell engager molecule that binds DLL3 and CD3.                                                                                     |
| Sponsor                                                                   | Amgen, Inc.                                                                                                                                     |
| ODE/Division                                                              | OOD/Division of Oncology 2                                                                                                                      |
| Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt) | October 27, 2023                                                                                                                                |

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

### **Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.**

- Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**  
Tarlatamab is indicated for the treatment of adult patients with extensive stage small cell lung cancer (SCLC), with disease progression on or after platinum-based chemotherapy.
- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**  
☐ YES ☒ NO
- Was the BTDR submitted to a PIND?**  
☐ YES ☒ NO  
If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

*If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:*

#### **4. Consideration of Breakthrough Therapy Criteria:**

- a. Is the condition serious/life-threatening<sup>1</sup>? ☒ YES ☐ NO

*If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:*

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<sup>1</sup> For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):
- i. Only animal/nonclinical data submitted as evidence ☐
  - ii. Insufficient clinical data provided to evaluate the BTDR  
(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
  - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
  - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
  - v. No or minimal clinically meaningful improvement as compared to available therapy<sup>2</sup>/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

**5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:**

*If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.*

*If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.*

**6. Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

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**Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.**

**7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

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<sup>2</sup> For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

### **Drug Description**

Tarlatamab is a half-life extended (HLE) bispecific T cell engager (BiTE®) that targets both delta-like ligand 3 (DLL3) on target cells and CD3 on T cells. The Sponsor states the pharmacologic effect of tarlatamab is mediated by specific redirection of previously primed cytotoxic CD8-positive or CD4-positive T lymphocytes to kill DLL3-positive cells.

### **Information regarding SCLC and the intended population for the proposed indication**

Small cell lung cancer (SCLC) accounts for approximately 15% of overall lung cancer cases with >330,000 new cases worldwide each year based on an estimated 2.2 million cases of lung cancer in 2020 (National Cancer Institute [NCI], 2023; National Organization for Rare Disorders [NORD], 2021; Sung et al, 2021). There are approximately 270,000 new deaths worldwide due to SCLC based on approximately 1.8 million lung cancer deaths in 2020 (Sung et al, 2021). SCLC 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 one radiotherapy field (limited stage), the majority of cases have disease diagnosed as extensive stage. Regardless of the stage at diagnosis, treatment is rarely curative, and SCLC is associated with poor long-term survival (5-year survival is <10%) (American Cancer Society, 2022).

DLL3 is expressed almost exclusively in the intracellular compartment of a few normal tissues but is upregulated and abnormally expressed on the cell surface of SCLC and other high-grade neuroendocrine tumors (Giffin et al, 2021; Owen et al, 2019). In an international noninterventional study to evaluate DLL3 prevalence, positive DLL3 expression was identified in 85% of patients with SCLC using immunohistochemistry (Rojo et al, 2020).

### **The drug's relation to existing therapy(ies)**

Current first-line treatment of extensive stage SCLC (ES-SCLC) generally consists of etoposide in combination with either cisplatin or carboplatin in combination with a programmed death ligand 1 (PD-L1) immune checkpoint inhibitor (atezolizumab or durvalumab) (National Comprehensive Cancer Network [NCCN] SCLC Guidelines, 2024). First-line regimens in extensive stage SCLC have a relatively high response rate of 60% to 70%, but nearly all patients relapse after initial therapy.

The preferred treatment option for patients in the relapsed or refractory setting is cytotoxic chemotherapy, including FDA-approved options of topotecan and lurbinectedin. See response in Section 9 for more detail.

Cytotoxic chemotherapies, such as topotecan and lurbinectedin, are expected to have differential tumor response based on a patient's "sensitivity" to platinum-based chemotherapy, and for cytotoxic chemotherapy regimens, efficacy is usually assessed separately in subgroups of platinum-sensitive or platinum-refractory. The platinum-sensitive subgroup is generally defined as responders who have disease progression  $\geq 90$  days after completion of first-line platinum-based chemotherapy, while the platinum-refractory subgroup is defined as patients who have no response or have an initial response to platinum-based chemotherapy but have progression <90 days after completion of first-line platinum-based chemotherapy. Given the mechanism of action of tarlatamab, sensitivity to platinum-based chemotherapy is not expected to impact response to tarlatamab.

## **8. Information related to endpoints used in the available clinical data:**

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
  - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
  - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

The Division considers ORR, when large in magnitude and/or associated with durable responses, an endpoint that is reasonably likely to predict clinical benefit for patients with SCLC who have progressed on or after platinum-based therapy. Clinically meaningful ORR with adequate duration of response has been used to support accelerated approval in this disease setting.

A statistically and clinically significant improvement in OS demonstrated in a randomized-controlled trial is considered a direct measure of the clinical benefit of a treatment in this disease and is an endpoint that could support traditional approval.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

**9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Topotecan is FDA approved for the treatment of patients with SCLC platinum-sensitive disease who progressed after first-line chemotherapy. The approval of topotecan was based on demonstration of similar OS with an improved toxicity profile compared to combination chemotherapy (cyclophosphamide, doxorubicin, and vincristine combination chemotherapy [CAV]). In the randomized study supporting approval, topotecan demonstrated an ORR of 24%, with a median DOR of 3.3 months. For the randomized study supporting approval, platinum-sensitive disease was defined as responders who progressed  $\geq 60$  days after completion of first-line therapy. Based on data from single arm studies using the more standard cut-off of  $\geq 90$  days for platinum-sensitive vs platinum-refractory, reported ORR ranged from 11% to 31% for patients with chemo-sensitive disease and 2% to 7% for patients with chemo-refractory disease.

Lurbinectedin received accelerated approval for treatment of metastatic SCLC with progression on or after platinum-based chemotherapy; this approval was based on an ORR of 30% (95% CI 22, 40) as assessed by independent review committee of and median DOR of 5.1 (95% CI 4.9, 6.4) months, with 35% of patients having DOR  $\geq 6$  months. ORR was 43% (95% CI 31, 57) in the platinum-sensitive subgroup and 13% (95% CI 5, 27) in the platinum-refractory subgroup.

In addition to topotecan and lurbinectedin, NCCN guidelines also list several other therapeutic options (not FDA-approved for patients who progress subsequent to initial systemic therapy such as taxanes, irinotecan, doxorubicin, etc. or retreatment with platinum-based chemotherapy for patients with platinum-sensitive disease (NCCN, 2024).

**10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation<sup>3</sup>.**

No other drugs have requested breakthrough therapy designation for the same indication or a very similar indication.

**11. Information related to the preliminary clinical evidence:**

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design<sup>4</sup>, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results. The primary support for this BTDR is based on the results from Study 20200491 which included patients with recurrent SCLC who had progressed or recurred after a platinum-based regimen (with or without checkpoint inhibitor) and at least one other line of therapy.

This study was conducted in three sequential parts:

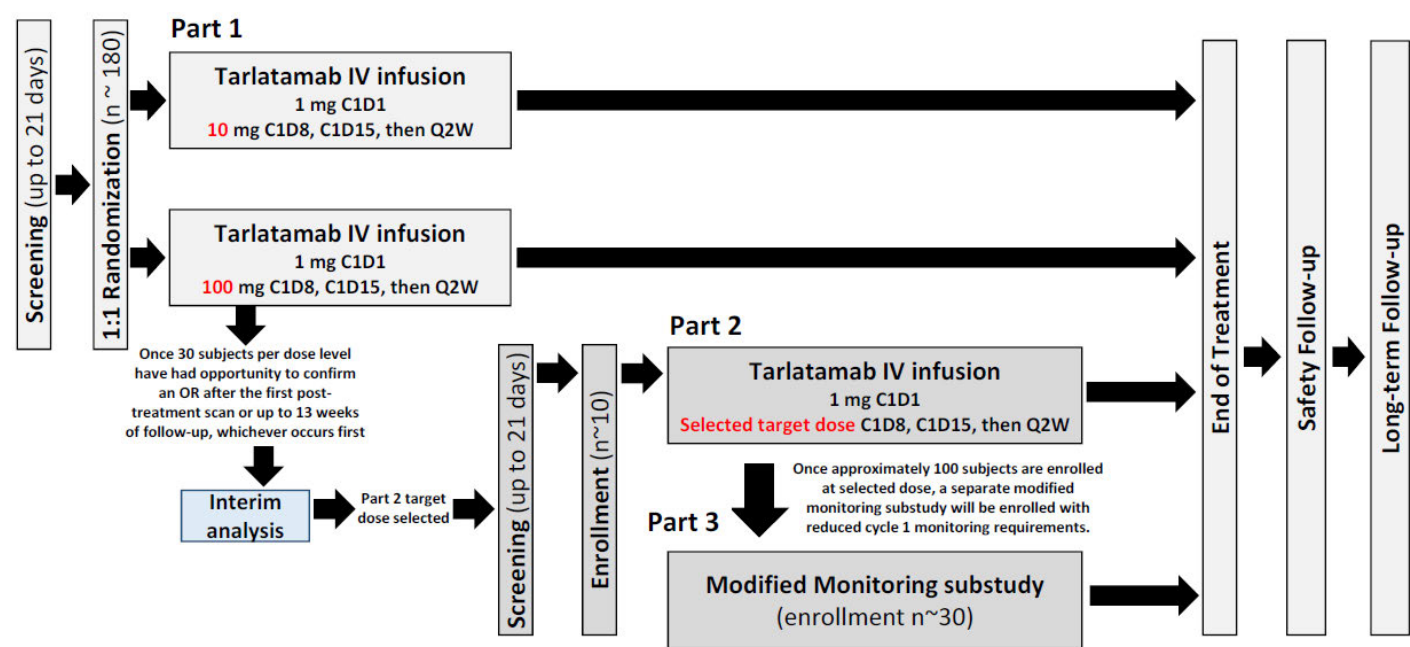
- Part 1 evaluated two dose levels of tarlatamab, with patients randomized 1:1 to treatment with target doses of 10 or 100 mg every two weeks (Q2W) [all treatment includes step-up dosing with 1 mg tarlatamab administered on C1D1 followed by administration of the target dose for subsequent doses starting C1D8]. An interim analysis was planned when 30 patients per arm reached sufficient follow-up to inform dose selection. Enrollment continued in a randomized fashion until the dose selection process was completed.
- Part 2 was a dose expansion phase that enrolled patients at the selected target dose based on the interim analysis of Part 1, until a total of 100 patients (combined from Parts 1 and 2) had been enrolled at the selected dose.
- Part 3 (ongoing) is designed to enroll approximately 30 additional patients at the selected dose, to evaluate modified cycle 1 monitoring criteria.

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<sup>3</sup> Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

<sup>4</sup> Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

**Figure 1. Pivotal Study: Study 20200491**  
**Population: Recurrent SCLC with progression after platinum and at least 1 other line of therapy**



As of June 27, 2023, 222 patients were randomized to Part 1 or enrolled to Parts 2 and 3 where 220 patients received at least one dose of tarlatamab (99 patients in the 10 mg target dose group across Parts 1 and 2, 87 in the 100 mg target dose group in Part 1, and 34 patients in the 10 mg target dose group in Part 3). The dose of 10 mg every 2 weeks was chosen as the dose for subsequent development based on higher efficacy and favorable safety profile at the 10 mg dose.

The primary ORR data supporting this BTDR is for 99 patients treated with the 10 mg target dose across Parts 1 and 2 of the trial. Mature data from Part 3 is not yet available. Of these 99 patients, 98% had received two or more prior lines of therapy and 32% had received three or more prior lines. The study population included patients with platinum-sensitive and platinum-refractory disease.

- Among the 99 patients in the 10 mg target dose group, **the ORR was 40% (95% CI 31, 51)** based on BIRC, including 1 patient (1%) with a complete response and 39 patients (39%) with a partial response. Of these 40 responders, 23 patients (58%) and 10 patients (25%) had a DOR of at  $\geq 6$  and  $\geq 9$  months, respectively. The median DOR was not estimatable (95% CI 6, NE).

(see response to Question 11b for summary of safety).

**Table 2. Clinical Data Supporting BTDR at the proposed recommended dose (10 mg target dose)**

| Study | Study Design | Part | No. of Patients | Results to support BTD |
|-------|--------------|------|-----------------|------------------------|
|       |              |      |                 |                        |

|                   |                                                                                                                                                                                                                                 |               |      |                                                                                                                                                        |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study<br>20200491 | Dose-finding and<br>activity estimating study<br><br>Primary endpoint: ORR<br>by BIRC<br><br>Population: patients pre-<br>treated (with or without<br>checkpoint inhibitor)<br>with platinum and one<br>other line of treatment | Parts 1 and 2 | N=99 | <b>ORR: 40% (95% CI 31, 51)</b><br>mDoR: NE (6, NE) months<br><br>For 40 responders:<br>% with DOR* $\geq$ 6 mos: 58%<br>% with DOR* $\geq$ 9 mos: 25% |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------|

\*Observed duration of response

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Tarlatamab demonstrated an ORR of 40% (95 CI 31%, 51%) in a population of patients which included patients with both platinum-sensitive and platinum-refractory disease. As noted above, given the mechanism of action of tarlatamab, sensitivity to platinum-based chemotherapy is not expected to impact response to tarlatamab; therefore, ORR is not presented for subgroups.

This data provides preliminary clinical evidence of a substantial improvement over available therapies when compared to FDA-approved therapies for relapsed/refractory ES-SCLC, which includes topotecan [ORR of 24% (95% CI 16, 32) for platinum-sensitive disease] and lurbinectedin [ORR 30% (95% CI 22, 40)]. . These data provide clinical evidence of a substantial improvement in ORR over available therapies in the relapsed or refractory setting.

#### *Safety data*

Safety data were provided for patients with SCLC (n=220) treated with tarlatamab at a dose of 10 mg and 100 mg IV on cycle 1 day 8, cycle 1 day 15 followed by every 2 weeks. The most frequently reported ( $\geq 20\%$  of patients) adverse events in Parts 1 and 2 (10 mg target dose, 100 mg target dose) were cytokine release syndrome (50%, 61%), pyrexia (38%, 33%), constipation (28%, 25%), anemia (26%, 25%), decreased appetite (25%, 44%), dysgeusia (24%, 14%), fatigue (21%, 20%), asthenia (20%, 24%), and COVID-19 (13%, 22%).

In Part 3, the most frequently reported ( $\geq 20\%$  of patients) adverse events by preferred term were CRS (56%), dysgeusia (41%), decreased appetite (38%), asthenia (29%), anemia and fatigue (each 27%), and pyrexia and constipation (each 24%).

When compared to the 100 mg dose, patients treated with the 10 mg dose had fewer Grade  $\geq 3$  TEAEs (58% versus 64%), fewer fatal adverse events (3% versus 6%), fewer serious adverse events (59% versus 71%) and adverse events that led to discontinuation of investigational product were similar in both dose groups (7% versus 7%). Similar results were also observed in the 10 mg target dose group with modified safety monitoring (Part 3).

## 12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting: DO2 recommends granting BTDR for the treatment of adult patients with extensive stage SCLC with disease progression on or after platinum-based chemotherapy.

Recurrent SCLC is a serious and life-threatening disease that is incurable with a high unmet medical need. In the context of a plausible biologic rationale and relevant mechanism of action, the observed ORR in patients in patients with extensive stage SCLC who have progressed on or after platinum therapy in Study 20200491 provides preliminary clinical evidence that tarlatamab provides a substantial benefit over available therapy based on the magnitude and duration of response.

The Division considers that the observed ORR, which is greater than the ORR reported for topotecan, the only FDA approved drug with traditional approval in a similar population, in association with DOR indicates that tarlatamab may demonstrate substantial improvement on a clinically meaningful endpoint(s) for patients with refractory/recurrent SCLC.

*Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

☐ DENY:

Provide brief summary of rationale for denial:

*Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:*

## 13. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

Amgen is submitting a BLA seeking accelerated approval for the same indication as proposed for BTDR. We have accepted the BLA submission for Real-Time Oncology Review program and have received the first two parts; the final submission is expected on 10/13/2023.

Amgen is also conducting Study 20210004, an ongoing global, open-label, randomized (b) (4) clinical trial comparing tarlatamab with standard of care treatment (topotecan, lurbinectedin, amirubicin) in patients with SCLC who have progressed after one prior line of platinum-containing therapy (b) (4) (b) (4) is intended to serve as the confirmatory trial to verify the clinical benefit of tarlatamab and support conversion to traditional approval for a second-line SCLC indication should accelerated approval be

granted based on Study 20200491. We met with Amgen to provide advice on the design of this study prior to its initiation.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

**14. List references, if any:**

1. American Cancer Society. Cancer Facts & Figures 2022. American Cancer Society, GA, USA (2022).
2. Giffin MJ, Cooke K, Lobenhofer EK, et al. AMG 757, a half-life extended, DLL3-targeted bispecific T-cell engager, shows high potency and sensitivity in preclinical models of small-cell lung cancer. Clin Cancer Res. 2021;27:1526-1537.
3. National Cancer Institute. PDQ Adult Treatment Editorial Board. Small cell lung cancer treatment. Bethesda, MD: Updated 02 March 2023. Available at <https://www.cancer.gov/types/lung/hp/small-cell-lung-treatment-pdq>
4. NCCN clinical practice guidelines in oncology for small cell lung cancer V.1.2024.
5. Owen DH, Giffin MJ, Bailis JM, Smit MD, Carbone DP, He K. DLL3: an emerging target in small cell lung cancer. J Hematol Oncol. 2019;12:61.
6. Rojo F, Corassa M, Mavroudis D, et al. International real-world study of DLL3 expression in patients with small cell lung cancer. Lung Cancer. 2020;147:23-243.
7. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249.

**15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?** YES ☒ NO ☐

**16. Clearance and Sign-Off (after MPC review):**

Grant Breakthrough Therapy Designation ☒  
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}  
Team Leader Signature: {See appended electronic signature page}  
Division Director Signature: {See appended electronic signature page}

**Revised 10/13/20 /M. Raggio**

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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.**  
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/s/  
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JEANNETTE C NASHED  
10/20/2023 10:31:26 AM

AMY K BARONE  
10/20/2023 12:04:09 PM

ERIN A LARKINS  
10/20/2023 01:02:54 PM  
Supervisory Associate Director, DO2, as designated signatory authority on behalf of Dr.  
Harpreet Singh



IND 134859

**MEETING MINUTES**

Amgen Inc.  
Attention: Claudia Arredondo Pimentel  
Senior Manager, Regulatory Affairs  
One Amgen Center Drive  
Thousand Oaks, CA 91320

Dear Ms. Arredondo Pimentel:<sup>1</sup>

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tarlatamab.

We also refer to the video conference between representatives of your firm and the FDA on September 8, 2023. The purpose of the meeting was to discuss the clinical and nonclinical aspects of the tarlatamab program in advance of submission of a planned Biologics License Application (BLA) for tarlatamab for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after (b) (4)

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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<sup>1</sup> 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](mailto: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



## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** September 8, 2023; 3:30 PM – 4:30 PM, EDT  
**Meeting Location:** Virtual Face-to-Face

**Application Number:** IND 134859  
**Product Name:** Tarlatamab  
**Indication:** Small Cell Lung Cancer  
**Sponsor Name:** Amgen Inc.  
**Regulatory Pathway:** 351(a) of the Public Health Service Act

**Meeting Chair:** Gautam Mehta, MD  
**Meeting Recorder:** Ashley Lane, MS

### FDA ATTENDEES

Erin Larkins, MD, Supervisory Associate Director, Division of Oncology 2 (DO2)  
Gautam Mehta, MD, Acting Cross Disciplinary Team Lead, DO2  
Yufan (Frank) Liu, PharmD, Clinical Analyst, DO2  
Anup Amatya, PhD, Acting Biostatistics Team Leader, Division of Biometrics V (DBV)  
Yi Ren, PhD, Biostatistics Reviewer, DB V  
Ashley Lane, MS, Senior Regulatory Health Project Manager, Division of Regulatory Operations

### SPONSOR ATTENDEES

Brian Abbott, BS, Executive Director, Regulatory Affairs  
Erik Anderson, MD, PhD, Medical Director, Clinical Research  
Claudia Arredondo Pimentel, BS, Senior Manager, Global Regulatory Affairs  
Michelle Geller, MD, Executive Medical Director, Global Patient Safety  
Giuseppe Giaccone, MD, PhD, Vice President, Global Development  
Jackie Kline, PhD, Vice President, Global Regulatory Affairs  
Pablo Martinez Rodriguez, MD, Executive Medical Director, Global Development  
Mukul Minocha, PhD, Associate Scientific Director, Clinical Pharmacology Modeling & Simulation  
Punam Bharania, MD, Medical Director, Global Patient Safety  
Vandana Pathak, MS, RAC, Director, Global Regulatory Affairs  
Tony Jiang, PhD, Director, Global Biostatistics

## BACKGROUND

### Meeting Purpose

On July 7, 2023, the FDA received a meeting request to discuss the clinical and nonclinical aspects of the tarlatamab program in advance of the planned Biologics License Application (BLA) for tarlatamab for the treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after (b) (4)

FDA sent Preliminary Comments to Amgen on September 6, 2023.

### Regulatory

FDA granted Orphan Drug designation to tarlatamab for the treatment of SCLC on December 27, 2018.

On September 2, 2021, a Type C meeting was held where the study design for Study 20200491 (two-part, open-label, international, multi-center, randomized trial comparing two dosages of tarlatamab in patients with SCLC with disease progression after at least two prior lines of therapy) was discussed. FDA indicated the design of Study 20200491 appeared acceptable in general and a determination of the adequacy of objective response rate (ORR) results from the trial to support a marketing application will depend on the magnitude and durability of the observed responses, in the context of the totality of the data including the toxicity profile. At this meeting, the designs of two potential randomized studies in patients with second-line SCLC which might be used to verify the clinical benefit of tarlatamab (including Study 20210004, described below) were also discussed.

On November 9, 2022, FDA communicated to Amgen via email that the 10 mg dose (with a step dose of 1 mg on treatment initiation) appears acceptable as the dose for continued study in Part 2 of Study 20200491 and for further evaluation for Phase 2 and Phase 3 trials in patients with relapsed/refractory SCLC.

On December 5, 2022, a Type B pre-phase 3 meeting was held where FDA stated that the study design for the proposed clinical trial, Study 20210004 (tarlatamab as a single agent for the treatment of patients with relapsed (b) (4) SCLC who have experienced disease progression after receiving one prior line of platinum-based therapy), which is intended to support traditional approval of tarlatamab for a second-line SCLC indication, may be adequate to support a marketing application provided the results demonstrate an improvement in overall survival (OS) with a positive benefit-risk assessment.

On February 6, 2023, a Type C meeting was held where the structure, format, and content of a proposed BLA for tarlatamab for the treatment of adult patients with

(b) (4) SCLC with disease progression on or after (b) (4) of therapy was discussed. FDA also provided feedback regarding the proposed principal concepts of the integrated summaries and the mock submission of electronic data.

## Nonclinical

Tarlatamab (AMG 757) is a half-life extended (HLE) bispecific T cell engager (BiTE®) comprised of single chain binding domains for delta-like ligand 3 (DLL3) and cluster of differentiation 3 (CD3) genetically fused to the N-terminus of a single chain IgG Fc region. Amgen has conducted in vitro and in vivo pharmacology studies, pharmacodynamic studies, and GLP-compliant repeat-dose toxicology studies of up to 3-month duration in monkeys. Safety pharmacology was integrated in the 28-day toxicology study. In addition, Amgen has conducted a non-GLP 28-day toxicology study in mice and an embryofetal development study in mice (ongoing) using the murine surrogate of tarlatamab, muS757.

## Clinical

Amgen intends to submit an original BLA seeking accelerated approval for tarlatamab for the treatment of adult patients with (b) (4) SCLC with disease progression on or after (b) (4) prior therapy. Amgen intends to seek Priority Review designation for this application along with participation in Project Orbis and the Real-Time Oncology Review (RTOR) program. Amgen proposes four batches of submission via RTOR with plans for the first batch to be submitted on September 11, 2023, and the final batch on October 13, 2023. The countries and respective timelines for submission proposed by Amgen for participation in Orbis are presented below.

| Proposed Country | Application Type | Planned Presubmission Meeting Date <sup>a</sup>                          | Proposed Orbis Type <sup>b</sup> | Planned MAA <sup>c</sup> Submission Date |
|------------------|------------------|--------------------------------------------------------------------------|----------------------------------|------------------------------------------|
| United States    | BLA (761344)     | 11 July 2023 (CMC; complete)<br>08 September 2023 (Clinical/Nonclinical) | Type A                           | October 2023                             |
| Canada           | (b) (4)          |                                                                          |                                  |                                          |
| Brazil           |                  |                                                                          |                                  |                                          |
| United Kingdom   |                  |                                                                          |                                  |                                          |
| Israel           |                  |                                                                          |                                  |                                          |
| (b) (4)          |                  |                                                                          |                                  |                                          |

Proposed Studies for inclusion in proposed BLA

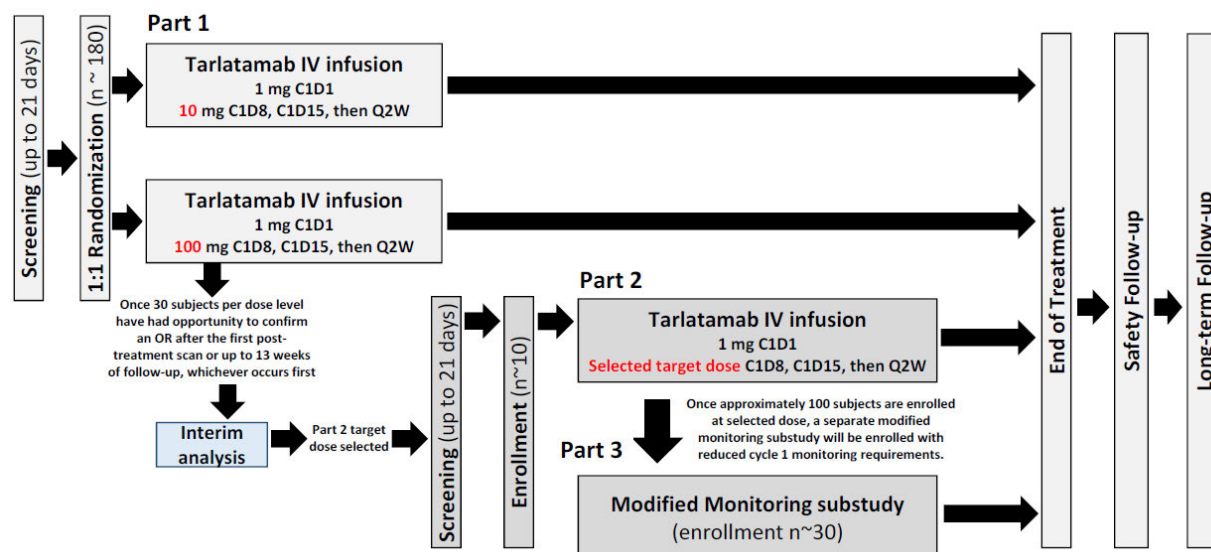
A summary of the primary and supportive studies planned for inclusion in the proposed BLA is provided in Table 1 below.

**Table 1: Overview of studies proposed for inclusion in BLA**

| Study number                                                                       | Study population                                                                                                                                                              | Study design and dose levels                                                                                                                                                                                                                                                                | Notes                                                                                             |
|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| <b>Primary study</b>                                                               |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                             |                                                                                                   |
| 20200491 (ongoing)<br><br>Global<br><br>N=100 at 10 mg dose<br>N=88 at 100 mg dose | Relapsed/refractory SCLC after two or more prior lines of treatment                                                                                                           | Part 1 – Randomized (10 mg vs. 100 mg) → Part 2 – Single arm dose expansion → Part 3 – Modified monitoring safety cohort                                                                                                                                                                    | Primary endpoints (Part 1): ORR by BICR, Safety and pharmacokinetics                              |
| <b>Supportive studies</b>                                                          |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                             |                                                                                                   |
| 20160323 (ongoing)<br><br>Global<br><br>N=17 at 10mg step dose                     | Dose escalation and expansion Cohort A and Dose escalation Cohort C: relapsed/refractory SCLC patients who progressed or recurred following at least 1 platinum-based regimen | Dose escalation Cohort A: doses from 0.003 mg to 100 mg tested<br><br>Dose expansion Cohort A: tested doses of 100 mg (with 1 mg step dose) and 100 mg over 3 days (extended IV infusion)<br><br>Dose escalation Cohort C: tested doses of 0.1 and 0.3 mg in combination with pembrolizumab | Provides supportive efficacy and safety data                                                      |
| (b) (4)                                                                            |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                             |                                                                                                   |
|                                                                                    |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                             |                                                                                                   |
| 20210004 (ongoing; planned N=700)<br><br>Global<br><br>N=9                         | Relapsed SCLC patients who progressed after 1 prior line of platinum-based therapy                                                                                            | Randomized: Tarlatamab vs. SoC (topotecan, lurbinectedin, amirubicin)                                                                                                                                                                                                                       | Primary endpoint: Overall survival<br><br>Inclusion in BLA to further characterize safety profile |

### Study 20200491 (Primary Trial) Topline Results

Study 20200491 is an ongoing, three-part, multi-center trial evaluating tarlatamab in patients with SCLC who have experienced disease progression after receiving at least two prior lines of therapy, including one platinum-based chemotherapy regimen. The aim of Part 1 was to evaluate two active doses of tarlatamab, of which the 10 mg step dose (1 mg dose on cycle 1 day 1, followed by 10 mg on cycle 1 day 8 and cycle 1 day 15, followed by 10 mg every 2 weeks onward) was selected as the dose to move forward. The aim of Part 2 is to further evaluate tarlatamab at the selected 10 mg dose level. Part 3 consists of a modified safety monitoring cohort to evaluate the safety of reduced inpatient monitoring with tarlatamab administration. The key efficacy endpoints for Parts 1 and 2 were overall response rate (ORR) and duration of response (DoR) by blinded independent central review (BICR) per RECIST 1.1. A study design figure is presented below.



As of June 27, 2023, 222 patients were enrolled and 220 patients had received at least one dose of tarlatamab in Study 20200491, including 99 patients in the 10 mg target dose group (i.e., the to-be-marketed dose) from Parts 1 and 2 and 34 patients in the 10 mg target dose group with modified safety monitoring from Part 3. Enrolled patients had received a median of two prior lines of therapy and the majority of patients (74%) had received prior anti-PD-(L)1 therapy.

In patients in the 10 mg target dose group treated in Parts 1 and 2 (n=99), the ORR was 40% (97.5% confidence interval [CI]: 29, 52) and median DoR was not estimable (NE) (95% CI: 5.9, NE). Of the 40 responders in the 10 mg target dose group, 23 patients (58%) had a DoR of  $\geq 6$  months. All patients in Parts 1 and 2 had the opportunity to have at least 24 weeks of follow-up from the first scheduled post-baseline tumor assessment and the median follow-up time for response was 8.3 months. Activity across subgroups is presented in the table below for the 10 mg step dose.

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| Subgroup results for 10 mg step dose       | ORR, % (95% CI) | Median DoR (95% CI) (months) |
|--------------------------------------------|-----------------|------------------------------|
| Overall (n=99)                             | 40% (31, 50)    | NE (5.9, NE)                 |
| Prior PD-(L)1 Therapy                      |                 |                              |
| Yes (n=72)                                 | 40% (29, 53)    | 7.6 (4.2, NE)                |
| No (n=27)                                  | 41% (22, 61)    | NE (6.9, NE)                 |
| Time to progression after platinum therapy |                 |                              |
| <90 days (n= 27)                           | 52% (32, 71)    | 5.9 (3.1, NE)                |
| ≥90 days (n= 42)                           | 31% (18, 47)    | NE (5.6, NE)                 |
| Unknown (n=30)                             | 43% (25, 63)    | NE (4.4, NE)                 |

The incidence of grade  $\geq 3$  adverse events (AEs) was 58% in the 10 mg target dose group. AEs that led to discontinuation of tarlatamab were reported for seven patients (7%) in the 10 mg target dose group. Serious AEs (SAEs) were reported in 59% of patients in the 10 mg target dose group. Three patients (3%) in the 10 mg target dose group had fatal AEs. Cytokine release syndrome (CRS) was reported in 50% of patients in the 10 mg target dose group; all AEs of CRS were grade 1 or 2 and none led to discontinuation of tarlatamab, but approximately 50% of these events were reported as SAEs. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 7% of patients. All ICANS AEs were grade 1 in severity with ICANS in two patients reported as SAEs, and one patient discontinued tarlatamab due to ICANS.

Efficacy data in the modified safety monitoring cohort (Part 3), was immature with a median follow-up time of 1.4 months. Grade  $\geq 3$  AEs occurred in 65% of patients, SAEs occurred in 41% of patients, AEs leading to discontinuation of tarlatamab occurred in three (9%) of the patients, and four patients had fatal AEs including one event of respiratory failure considered related to tarlatamab by investigator.

Status of Study 20210004 (Phase 3 trial intended to verify clinical benefit)

Study 20210004 is an ongoing randomized, active-controlled, two-arm clinical trial of tarlatamab as a single agent versus standard of care (investigator's choice) in patients with relapsed (b) (4) SCLC with disease progression after one prior line of platinum-based therapy.

(b) (4)

## SPONSOR QUESTIONS AND FDA RESPONSES

### Nonclinical

1. Does the Agency agree with the proposed nonclinical content in support of the BLA submission for the proposed indication?

**FDA Response:** We agree that the described nonclinical data package appears sufficient to support the submission of a marketing application. Final determination of the adequacy of the data from these studies to support a marketing application in the proposed indication will be made following their review.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's feedback.

**Discussion During Meeting:** Discussion during meeting did not occur.

### Clinical

2.
  - a. Does the Agency agree that the totality of evidence, including clinical efficacy and safety data, provide an adequate basis for BLA submission under accelerated approval regulations (21 CFR 314 Subpart H) for tarlatamab monotherapy for the proposed indication?

**FDA Response:** We agree that the data provided appears adequate to support filing of a BLA.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's feedback.

**Discussion During Meeting:** Discussion during meeting did not occur.

- b. Additionally, given the available clinical efficacy data from the registrational phase 2 Study 20200491 and overall safety data, does the Agency consider the data supportive of tarlatamab monotherapy approval under accelerated approval regulations (21 CFR 314 Subpart H) for the indication "treatment of adult patients with advanced SCLC with disease progression on or after (b) (4)."?

**FDA Response:** A determination regarding approvability will be made during BLA review. Please modify your proposed indication statement to specify that patients must have progressed on prior platinum-based chemotherapy. The wording of the indication statement will be a review

issue, and a final determination of the indication will be made during review of the application.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's feedback. Amgen will update the indication to "Treatment of adult patients with advanced small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy".

**Discussion During Meeting:** Discussion during meeting did not occur.

3. **Does the Agency agree with the proposal for the efficacy update report to be submitted with 90-day safety update and that submission of the updated efficacy data will not impact the BLA review timeline and the PDUFA action date?**

**FDA Response:** While it would be acceptable to provide updated efficacy data in the 90-day safety update report, previous assessments of response should not be re-adjudicated. This means that ORR results should not change unless a new response occurred after the original data cut-off date and updated duration of response for responses documented prior to the original cut-off date should be based on date of response used for the initial BLA submission.

In general, submission of updated efficacy data with the 90-safety update report alone would not be expected to impact the PDUFA action date, provided there are not substantial changes that would impact assessment of the risk:benefit of tarlatamab for the proposed indication.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's feedback and confirms that no re-adjudication of previous assessment of response made at the time of primary analysis (PA) data cut-off (DCO) date (27 June 2023) will be included in the updated efficacy data planned to be submitted with 90-day safety update report.

For the purpose of transparency, Amgen was made aware of an unsubmitted progressive disease scan for subject (b) (6) (100 mg dose) on (b) (6) before PA DCO. This was communicated to Amgen after data base lock. In the current snapshot, this subject is captured as a confirmed PR with DoR censored at 7 month, but with this new scan the DoR assessment has changed from censored to event. This PD scan, if incorporated, has no impact on ORR (still a PR as best overall response), median DoR, and median PFS for 100 mg, and does not impact 10 mg dose group at all.

**Discussion During Meeting:** Discussion during meeting did not occur.

## Clinical Safety

4. Does the Agency agree that a Risk Evaluation and Mitigation Strategy (REMS) or Medication Guide would not be considered necessary to support the BLA submission for the proposed indication?

**FDA Response:** It is premature to make a final assessment whether a REMS would be necessary. A final determination will be made during BLA review.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's feedback.

**Discussion During Meeting:** Discussion during meeting did not occur.

## Regulatory

5. Does the Agency concur that an agreed iPSP is not required prior to the submission of the planned BLA?

**FDA Response:** Given our prior correspondence, we agree that an agreed iPSP is not required given that tarlatamab has Orphan Drug designation for the treatment of SCLC.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's feedback.

**Discussion During Meeting:** Discussion during meeting did not occur.

6. Does the Agency agree that the clinical safety and efficacy data from the phase 2 Study 20200491 and the supporting studies provide an adequate basis for Priority Review?

**FDA Response:** Determinations regarding Priority Review designation are made after submission of the marketing application.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's feedback and confirm that the Priority Review designation application will be included with the BLA submission.

**Discussion During Meeting:** Discussion during meeting did not occur.

7.

- a. **Does the Agency agree that the planned BLA could qualify for participation in the RTOR pilot program? If yes, does the Agency agree with the proposed content and timelines of the presubmission batches?**

**FDA Response:** We agree that the planned BLA qualifies for participation in the RTOR program. We have no objections to the proposed content and timelines for the pre-submission batches; however, we recommend that submission documents involving Chemistry, Manufacturing, and Controls be included in earlier submission batches if possible to enable a more efficient review.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's feedback and confirms that documents from Module 3 Chemistry, Manufacturing, and Controls are planned to be included in earlier pre-submission batches. A detailed TOC for each pre-submission batch is included as Appendix 1.

**Discussion During Meeting:** Discussion during meeting did not occur.

- b. **Given the top-line results from the pivotal phase 2 Study 20200491, can the Agency advise if the planned BLA could be selected for Project Orbis? In the event 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 BLA be selected for participation in Project Orbis. We will communicate the countries that would participate in Project Orbis in approximately one month after receipt of the global submission plan.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's feedback. Global submission plan will be sent by email followed by a formal submission on 08 September 2023.

**Discussion During Meeting:** Discussion during meeting did not occur.

## Multidisciplinary

8. **Amgen considers that the overall status of the confirmatory Study 20210004 supports the submission of the BLA at the planned timeline. Does the Agency agree?**

**FDA Response:** The confirmatory trial to verify clinical benefit should be well underway, if not fully enrolled, at the time of accelerated approval. Please provide your enrollment projections, including the number of patients anticipated to be randomized in your confirmatory study at the time of potential initial BLA approval. In addition, if the trial is anticipated to still be enrolling patients at the time of potential accelerated approval, please provide post-approval enrollment targets and your plan of action for enrollment, including in the United States, if accelerated approval is granted.

Whether your confirmatory trial enrollment is considered adequate will be a review issue and will depend on the enrollment status of the trial, including the pace of enrollment for your trial and planned enrollment projections.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's feedback. Provided below is an update on the current enrollment status of Study 20210004 (confirmatory trial) and projected enrollment covering various anticipated time of accelerated approval through full enrollment. Based on the Primary Analyses data from Study 20200491 (b) (4)



9. Does the Agency agree with the proposal for the data package in a Study Standardized Plan?

**FDA Response:** Yes, we agree.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's feedback.

**Discussion During Meeting:** Discussion during meeting did not occur.

#### **ADDITIONAL FDA COMMENTS**

##### **Clinical**

10. In your BLA submission, please provide a full list of prior therapies received, including the number (and percentage) of patients who received prior treatment

with specific agents (e.g., anti-PD-(L)1 therapy, topotecan, irinotecan, lurbinectedin).

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's comment and will include this in the BLA submission.

**Discussion During Meeting:** Discussion during meeting did not occur.

11. In your confirmatory trial, we recommend that adequate monitoring and mitigation measures are in place to ensure there are not a substantial number of patients who withdraw consent and/or are lost to survival follow-up.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's comment and will take this into consideration.

**Discussion During Meeting:** Discussion during meeting did not occur.

12. A large proportion of patients (approximately 30%) in Study 20200491 have an unknown time to disease progression after platinum therapy and their disease cannot be categorized as either platinum-resistant or platinum-sensitive. We recommend that you retrospectively review these patients' charts to provide this clinical information in your BLA submission. In addition, please update the subgroups for platinum sensitivity to <90 days and ≥90 days for your BLA submission.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's comment and will include these analyses in the BLA submission.

**Discussion During Meeting:** Discussion during meeting did not occur.

13. For the ORR estimates, please provide a 95% confidence interval using the Clopper-Pearson exact method.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's comment and will include this in the BLA submission.

**Discussion During Meeting:** Discussion during meeting did not occur.

14. We recommend that the as-treated population, which includes all patients who received at least one dose of tarlatamab, be the efficacy analysis population for Study 20200491. Please confirm that all patients who were treated with at least one dose of tarlatamab were included in the efficacy population.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges FDA's comment.

The current efficacy analysis of ORR and DoR is based on BICR full analysis set which includes all subjects from part 1 and 2, who have received one dose of tarlatamab and have one or more measurable lesion at baseline per BICR (SAP version 6.0 submitted on 17 July 2023 SN 0146).

Of 186 subjects who have received at least one dose of tarlatamab in part 1 and 2, 185 subjects are included in the BICR full analysis set.

There is only one subject from 100 mg who is not deemed measurable by BICR. This subject has a best overall response of complete response.

Amgen proposes to do a post-hoc analysis on ORR and DoR using all subjects who were treated, which would have no impact on 10 mg, and with one more CR patient added in the 100 mg comparing with the primary analysis.

**Discussion During Meeting:** FDA noted that in general FDA prefers that the as treated population be considered the primary efficacy population; however, Amgen's approach appears acceptable in this case.

15. Please add sex and ECOG performance status to your subgroup analyses for efficacy and safety.

**Amgen's Response Received via Email on September 7, 2023:** Amgen acknowledges the FDA's comment and will add this to the subgroup analyses for efficacy and ISS.

**Discussion During Meeting:** Discussion during meeting did not occur.

## **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed. Reference the discussion on the contents of a complete application as captured in the above Meeting Minutes.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- FDA will make a final determination regarding the need for REMS during the review of the BLA.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, FDA issued a Written Response for a chemistry pre-submission meeting on July 20, 2023. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

### **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) 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 draft 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](https://www.fda.gov).<sup>2</sup>

## **FDARA REQUIREMENTS**

Sponsors 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](mailto:OCEPERC@fda.hhs.gov). For further guidance on pediatric product development, please refer to [FDA.gov](https://www.fda.gov).<sup>3</sup>

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<sup>2</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

<sup>3</sup> <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

## **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<sup>4</sup> and Pregnancy and Lactation Labeling Final Rule<sup>5</sup> 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

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<sup>4</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

<sup>5</sup> <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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 with the format items in regulations and guidances.

### **DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS**

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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## **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](mailto: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).

## **OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those 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). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.<sup>6</sup>

## **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

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<sup>6</sup> <https://www.fda.gov/media/85061/download>

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, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR<sup>7</sup>: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid<sup>8</sup>

### **NONPROPRIETARY NAME**

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

### **SUBMISSIONS WITH REAL-WORLD EVIDENCE**

CDER strongly encourages sponsors to identify 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

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<sup>7</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

<sup>8</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products*.<sup>9</sup> For questions or clarification, contact [cdernmedicalpolicy-realworldevidence@fda.hhs.gov](mailto:cdernmedicalpolicy-realworldevidence@fda.hhs.gov).

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<sup>9</sup> <https://www.fda.gov/media/124795/download>

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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.**  
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/s/  
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**MEETING MINUTES**

Amgen Inc.  
Attention: Sunyoung Lee, MS, PhD  
Director, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop: 27-2-D  
Thousand Oaks, CA 91320

Dear Dr. Lee:<sup>1</sup>

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tarlatamab.

We also refer to the video conference between representatives of your firm and the FDA on February 6, 2023. The purpose of the meeting was to discuss the proposed structure, format, and content of a proposed Biologics License Application for tarlatamab for the treatment of adult patients with (b) (4) small cell lung cancer with disease progression on or after (b) (4) lines of therapy. Additionally, you are seeking feedback on the proposed principal concepts of the integrated summaries and feedback on the mock submission of electronic data.

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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<sup>1</sup> 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](mailto:Ashley.Lane@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Ashley Lane, MS  
Consumer Safety Officer  
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

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type C  
**Meeting Category:** Guidance

**Meeting Date and Time:** February 6, 2023; 3:00 PM – 4:00 PM, EST  
**Meeting Location:** Virtual Face-to-Face

**Application Number:** IND 134859  
**Product Name:** Tarlatamab  
**Indication:** Small cell lung cancer  
**Sponsor Name:** Amgen Inc.  
**Regulatory Pathway:** 351(a) of the Public Health Service Act

**Meeting Chair:** Oladimeji Akinboro  
**Meeting Recorder:** Ashley Lane

### CDER Participants (tentative):

Erin Larkins, MD, Acting Supervisory Associate Director, Division of Oncology 2 (DO2)  
Oladimeji Akinboro, MD, Acting Cross Disciplinary Team Lead, DO2  
Yufan Liu, MD, Clinical Reviewer, DO2  
Claudia Miller, PhD, Acting Nonclinical Team Leader, Division of Hematology Oncology Toxicology (DHOT)  
Stephanie Aungst, PhD, Nonclinical Reviewer, DHOT  
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Team Leader, Division of Cancer Pharmacology II (DCP II)  
Lingshan Wang, PhD, Clinical Pharmacology Reviewer, DCP II  
Pallavi Mishra-Kalyani, PhD, Biostatistics Team Leader, Division of Biometrics V (DBV)  
Somak Chatterjee, PhD, Biostatistics Reviewer, DBV  
Ashley Lane, MS, Consumer Safety Officer, Division of Regulatory Operations

### SPONSOR ATTENDEES

Giuseppe Giaccone, Vice President, Global Development  
Danielle Jandial, Executive Medical Director, Global Development  
Pablo Martinez, Executive Medical Director, Global Development  
Erik Anderson, Medical Director, Clinical Research Medical  
Ramachandran Suresh, Executive Director, Biostatistics  
Alicia Zhang, Director, Biostatistics  
Michelle Geller, Medical Executive Director, Global Safety  
Sujoy Mukherjee, Medical Director, Global Safety  
Arju Sangal, Medical Director, Global Safety  
Daisy Wang, Director, Biostatistical Programming  
Qing Yu, Senior Manager, Biostatistical Programming

Jackie Kline, Vice President, Regulatory Affairs  
Brian Abbott, Executive Director, Regulatory Affairs  
Sunyoung Lee, Director, Regulatory Affairs  
Claudia Arredondo, Senior Manager, Regulatory Affairs

## BACKGROUND

### Meeting Purpose

On November 23, 2022, FDA received a Type C meeting request from Amgen to discuss the proposed structure, format, and content of a proposed Biologics License Application (BLA) for tarlatamab for the treatment of adult patients with (b) (4) small cell lung cancer (SCLC) with disease progression on or after (b) (4) lines of therapy. Additionally, Amgen is seeking feedback on the proposed principal concepts of the integrated summaries and feedback on the mock submission of electronic data.

FDA sent Preliminary Comments to Amgen on February 1, 2023.

### Regulatory

FDA granted Orphan Drug designation to tarlatamab for the treatment of SCLC on December 27, 2018.

On September 2, 2021, a Type C meeting was held where the study design for Study 20200491 (two-part, open-label, international, multi-center, randomized trial comparing two dosages of tarlatamab in patients with SCLC with disease progression after at least two prior lines of therapy) was discussed. FDA indicated the design of Study 20200491 appeared acceptable in general and a determination of the adequacy of objective response rate (ORR) results from the trial to support a marketing application will depend on the magnitude and durability of the observed responses, in the context of the totality of the data including the toxicity profile. At this meeting, the designs of two potential randomized studies in patients with second-line SCLC which might be used to verify the clinical benefit of tarlatamab (including Study 20210004 described below) were also discussed.

On November 9, 2022, FDA communicated to Amgen via email that the 10 mg dose (with a step dose of 1 mg on treatment initiation) appears acceptable as the dose for continued study in Part 2 of Study 20200491 and for further evaluation for Phase 2 and Phase 3 trials in patients with relapsed/refractory SCLC.

On December 5, 2022, a Type B pre-phase 3 meeting was held where FDA stated that the study design for the proposed clinical trial, Study 20210004 (tarlatamab as a single agent for the treatment of patients with relapsed (b) (4) SCLC who have experienced disease progression after receiving one prior line of platinum-based

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Silver Spring, MD 20993  
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therapy), which is intended to support regular approval of tarlatamab for a second-line SCLC indication, may be adequate to support a marketing application provided the results demonstrate an improvement in overall survival (OS) with a positive benefit-risk assessment.

## Nonclinical

Tarlatamab is a half-life extended (HLE) bispecific T cell engager (BiTE®) comprised of single chain binding domains for DLL3 and CD3 genetically fused to the N-terminus of a single chain IgG Fc region. The HLE moiety is capable of binding to the neonatal Fc receptor (FcRn) thereby prolonging the serum half-life of the protein. The activity of tarlatamab requires the simultaneous binding to both target cells (DLL3+) and T cells. The pharmacological effect is mediated by redirection of CD8+ or CD4+ T lymphocytes to kill DLL3+ cells. Amgen has conducted several in vitro and in vivo pharmacology studies and a 28-day safety pharmacology study and GLP-compliant repeat-dose toxicology studies of 1-month and 3-month duration, all in cynomolgus monkeys, using tarlatamab. In addition, using a murine surrogate of tarlatamab (muS757), Amgen conducted an embryofetal development study, a mouse juvenile toxicology study, and a non-GLP compliant 1-month repeat-dose toxicology study in mice.

## Clinical Pharmacology

Serum tarlatamab exposures increased in an approximately dose-proportional manner from doses of 0.003 to 100 mg based on preliminary pharmacokinetic (PK) data from 153 patients with SCLC from Study 20160323. Mean estimated elimination half-life ranged from 3.7 to 8.3 days. Steady-state serum tarlatamab exposures were achieved within 4 weeks of every other week dosing.

Amgen intends to utilize data from Studies 20160323 and 20200491 for the population pharmacokinetics (popPK) analysis. For population exposure-response analysis, Amgen intends to utilize data from Studies 20160323 and 20200491 for key safety variables and Study 20200491 for efficacy variables. Given the differences in the grading criteria, the data for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) and Associated Neurological events will only be provided in 20160323 and 20200491 Clinical Study Reports (CSRs) instead of included in the pooled analysis for key safety variables. Amgen proposes to submit merged non-linear mixed effects modeling (NONMEM) datasets that include all pertinent PK and exposure-response data from the above-mentioned studies.

Amgen proposes to provide a summary of immunogenicity, which will include an overview of the immunogenicity results from Study 20160323 and Study 20200491 for tarlatamab monotherapy. Associated analytical methods, immunogenicity monitoring strategy and associated details of the validated assays, and CSRs will also be included. The impact of immunogenicity on PK, efficacy and safety parameters will also be evaluated and discussed.

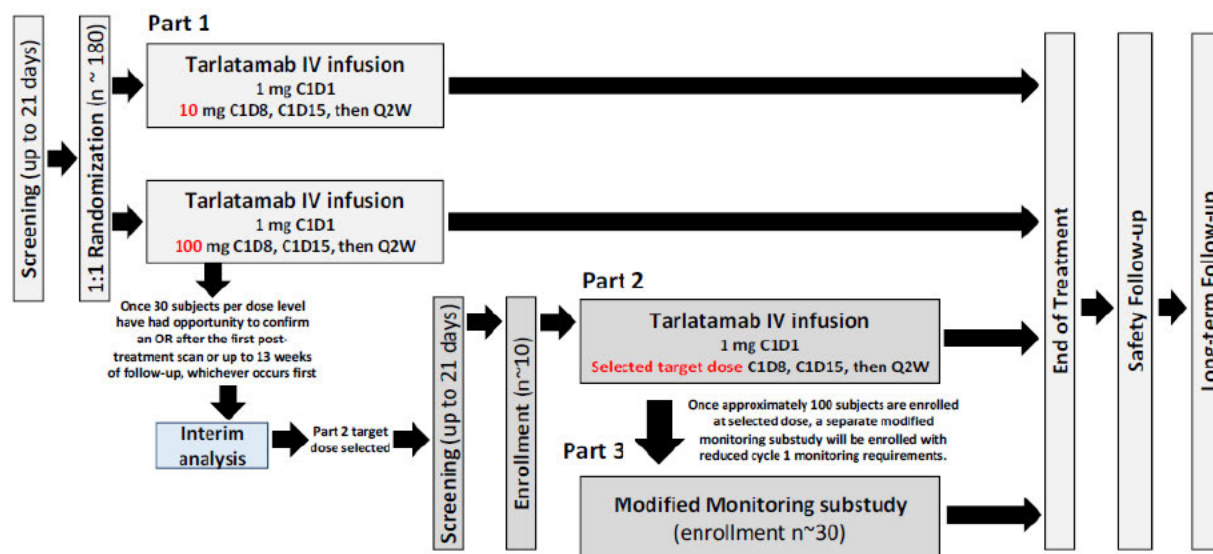
## Clinical

Amgen intends to submit an original Biologics License Application (BLA) seeking accelerated approval for tarlatamab for the treatment of adult patients with (b) (4) small cell lung cancer (SCLC) with disease progression on or after (b) (4) of therapy. Amgen anticipates submission of the proposed BLA in the fourth quarter of 2023.

### Study 20200491: Trial intended to support marketing application for potential accelerated approval

Amgen proposes to submit results from Study 20200491 as the primary efficacy data to support a marketing application for potential accelerated approval for tarlatamab. Study 20200491 is an ongoing, three-part, multi-center trial evaluating tarlatamab in patients with SCLC who have experienced disease progression after receiving at least two prior lines of therapy, including one platinum-based chemotherapy regimen and an anti-PDL1 antibody (in countries where these antibodies are available as part of the standard of care [SOC] treatment for SCLC). Part 1 will enroll approximately 180 patients to be randomized 1:1 to receive tarlatamab at one of two dose levels: 10 mg or 100 mg. Part 2 will be a dose expansion phase at the selected target dose and enroll approximately 10 patients to reach a total of approximately 100 patients (from Parts 1 and 2 combined) treated at the selected dose level. The primary endpoint for Parts 1 and 2 is overall response rate (ORR). Part 3 is a safety monitoring substudy that will be conducted after enrollment of Parts 1 and 2 has been completed. Part 3 will enroll approximately 30 additional patients at the 10 mg dose, with modified safety monitoring in Cycle 1.

A study schema is provided below.



Source: Figure 2, Meeting package, Page 26

Study (b) (4) Proposed confirmatory trial to verify clinical benefit of tarlatamab  
Amgen proposes to conduct Study 20210004 as a global, open-label, randomized,  
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active control study comparing tarlatamab with standard of care treatment (topotecan, lurbinectedin, amirubicin) in patients with SCLC who have progressed after one prior line of platinum-containing therapy. Amgen intends Study [REDACTED] (b) (4) to serve as the confirmatory trial to verify the clinical benefit of tarlatamab and support conversion to regular approval. The primary endpoint is overall survival (OS) and study initiation is planned in May 2023.

Proposed Studies for inclusion in proposed BLA

A summary of the primary and supportive studies planned for inclusion in the proposed BLA is provided in Table 1 below.

**Table 1: Overview of studies proposed for inclusion in BLA**

| Study number                                                                                                 | Study population                                                                                                                                                              | Study design and dose levels                                                                                                                                                                                                                                                                | Notes                                                                                             |
|--------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| <b>Primary study</b>                                                                                         |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                             |                                                                                                   |
| 20200491 (ongoing)<br><br>Global<br><br>N=100 at the selected dose level (10 mg)<br>N=X at 100 mg dose level | Relapsed/refractory SCLC after two or more prior lines of treatment                                                                                                           | Part 1 – Randomized (10 mg vs. 100 mg) → Part 2 – Single arm dose expansion → Part 3 – Modified monitoring safety cohort                                                                                                                                                                    | Primary endpoints (Part 1): ORR by BICR, Safety and PK                                            |
| <b>Supportive studies</b>                                                                                    |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                             |                                                                                                   |
| 20160323 (ongoing)<br><br>Global<br><br>Cohort A: N=181 as of July 2022<br><br>Cohort C: N=10                | Dose escalation and expansion Cohort A and Dose escalation Cohort C: relapsed/refractory SCLC patients who progressed or recurred following at least 1 platinum-based regimen | Dose escalation Cohort A: doses from 0.003 mg to 100 mg tested<br><br>Dose expansion Cohort A: tested doses of 100 mg (with 1 mg step dose) and 100 mg over 3 days (extended IV infusion)<br><br>Dose escalation Cohort C: tested doses of 0.1 and 0.3 mg in combination with pembrolizumab | Provides supportive efficacy and safety data                                                      |
| (b) (4)                                                                                                      |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                             |                                                                                                   |
|                                                                                                              |                                                                                                                                                                               |                                                                                                                                                                                                                                                                                             |                                                                                                   |
| 20210004 (planned; N=700)<br><br>Global                                                                      | Relapsed (b) (4) SCLC patients who progressed after 1 prior line of platinum-based therapy                                                                                    | Randomized: Tarlatamab vs. SoC (topotecan, lurbinectedin, amirubicin)                                                                                                                                                                                                                       | Primary endpoint: Overall survival<br><br>Inclusion in BLA to further characterize safety profile |

*Adapted from: Meeting package, Page 31*

Proposed Safety Reporting in the Clinical Study Reports (CSRs) for Studies 20160323 and 20200491:

- Amgen proposes to use a data cutoff (DCO) date of March 28, 2023, for all phase 1 data (20160323) as well as for PK and patient-reported outcome (PRO) data. For Study 20200491 efficacy, safety and PRO data, a DCO date of June 28, 2023, is planned to be used for the primary analysis. The proposed CSR headers are presented below.
- For Study 20200491, the primary analysis is planned when all patients (approximately 100 patients at the selected dose) have had the opportunity to have at least 6 months follow-up from the first baseline tumor assessment.

Proposed Content of the Integrated Summary of Efficacy (ISE):

- Efficacy results from Study 20200491 will be presented as the primary efficacy data to support the proposed indication and will not be pooled with efficacy data from any other ongoing tarlatamab monotherapy or combination studies. Therefore, Amgen proposes to not conduct an ISE analysis.
- Results from Study 20160323 will be included to provide supportive efficacy data.
- As part of the 90-day safety update, Amgen plans to submit updated efficacy data (Parts 1 and 2 of Study 20200491) which will include updated duration of response, progression-free survival, and overall survival for the efficacy patients included in the initial BLA submission. Amgen proposes to include this updated efficacy data in the tarlatamab USPI.

Proposed Content of the Integrated Summary of Safety (ISS):

- The primary safety population will be derived from patients enrolled in Studies 20160323 and 20200491 who received tarlatamab at the intended dose for the application (1-step 10 mg), at the 100 mg dose (supportive) and monotherapy overall. The proposed ISS headers are provided below

**Table 7. Proposed Table Header for Integration of Phase 1 and Phase 2 SCLC Population with Tarlatamab Monotherapy for ISS**

| <b>1-&gt;10 mg</b> | <b>1-&gt;100 mg</b> | <b>Overall Monotherapy</b> |
|--------------------|---------------------|----------------------------|
| <b>(N = xx)</b>    | <b>(N = xx)</b>     | <b>(N = xx)</b>            |
| <b>n (%)</b>       | <b>n (%)</b>        | <b>n (%)</b>               |

**1->10 mg** includes Study 20160323 cohorts 8 and 32 and Study 20200491 1->10 mg arm; **1->100 mg** includes Study 20160323 cohorts 10, 30, 11 only: tarlatamab + dexamethasone, and Study 20200491 1->100 mg arm; **Overall Monotherapy** includes all subjects in Study 20200491 and all subjects in Study 20160323 except for those in cohorts 15 and 16 (combination with pembrolizumab)

Source: Table 7, Meeting package, Page 30

- Amgen proposes to provide, in Module 5, [REDACTED] (b) (4) [REDACTED] but not to pool the data with the safety data from Studies 20160323 and 20200491.
- Safety evaluation to be summarized will include:
  - All treatment-emergent adverse events (TEAEs), treatment-related TEAE, serious TEAEs, Grade  $\geq 3$  TEAEs, fatal TEAEs, TEAEs leading to treatment interruption, TEAEs leading to dose reduction, and TEAEs leading to treatment discontinuation. TEAEs are defined as AEs that occur up to and including 42 days after the last dose of tarlatamab or end of study date, whichever is sooner.
  - Events of Interest, electrocardiogram results, clinical laboratory tests, physical measurements and vital signs
- Amgen plans to submit a 90-day safety update that will include:
  - An updated ISS of all patients from Studies 20160323 and 20200491 included in the primary analysis
  - New safety narratives for ongoing studies and updates to previously submitted safety narratives
- Studies 20160323 and 20200491 used different CTCAE versions for grading of adverse events. However, Amgen proposes to pool AEs (without harmonizing CTCAE grading used) except for CRS and ICANS and associated neurological events in the ISS given the differences in grading criteria for these events. Amgen proposes that the data for CRS, ICANS and associated neurological events will only be provided in the respective study CSRs. All AEs including CRS, ICANS and associated neurological events will be described in the summary of clinical safety.
  - An Amgen MedDRA Query for ICANS and Associated Neurological events has been created to include preferred terms to be used for the study CSRs
- Amgen proposes to submit safety narratives for patients with events that meet any of the following criteria below from Studies 20160323 and 20200491:
  - SAEs (including AEs leading to outcome of death)
  - AEs associated with study discontinuation
- Amgen proposes that the efficacy data from Part 3 of Study 20200491 (modified safety monitoring cohort) will not be included in the initial BLA submission, since at the time of DCO for the primary analysis, approximately 30 patients are expected to be enrolled with an estimated median follow up of 3 months. Amgen proposes to include safety data from this cohort in the initial BLA submission and the 90-day safety update report.

## SPONSOR QUESTIONS AND FDA RESPONSES

### Clinical Data Presentation in the Planned BLA

#### 1. Duration of Efficacy and Safety Data Collection

Currently, the phase 2 registrational Study 20200491 protocol specifies that the primary analysis is planned when all subjects have been enrolled (approximately 100 subjects at the selected dose) and have had the opportunity to have at least 6 months of follow-up from the first post-baseline tumor assessment. Primary analysis (PA) will be based on the disease response assessment by blinded independent central review (BICR) per RECIST 1.1. Amgen proposes that the primary analyses be planned after at least 24 weeks of follow-up (instead of 6 months [26 weeks]) from the first post-baseline tumor assessment to align with Q6W imaging schedule. The proposed CSR header is presented in Section 3.1.

**Does the agency agree with the proposed follow-up duration for efficacy and safety data collection in the BLA?**

**FDA Response:** In general, we would recommend the primary analysis be timed to provide follow-up of 6 months past onset of response for all responders. However, if almost all responses are occurring by the time of the first post-baseline tumor assessment, your proposal to conduct the primary analyses after at least 24 weeks of follow-up from the first post-baseline tumor assessment may be acceptable. A determination of whether the proposed follow-up is appropriate to support a BLA submission will be made at the time of a pre-BLA meeting when topline data are available.

In addition, please provide justification for increasing patient enrollment in Part 1 of Study 20200491 from 120 to 180 patients to be randomized 1:1 between two doses and decreasing the enrollment in Part 2 of the study from 40 to 10 patients in the most recently updated protocol version (received by FDA on December 22, 2022), given the prior communication from FDA on November 9, 2022, indicating that the 10 mg dose appears acceptable for evaluation in Part 2 of Study 20200491. This proposed increased patient enrollment may result in the unnecessary exposure of additional patients to the 100 mg dose of tarlatamab in Part 1 and presents a safety concern given the toxicity of tarlatamab.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's response that 24-week follow-up from first post-baseline tumor assessment may be acceptable.

Regarding the estimated enrollment numbers, Amgen acknowledges the update in estimation of enrolled patients on 20200491 Part 1 in the most recent protocol

amendment. The original protocol design for this study outlined that Part 1 enrollment would continue during the interim analysis and dose selection process. The target enrollment (n=30 subjects at each dose) for the interim analysis was met on 15 Jun 2022, with interim analysis date defined by each subject having the opportunity to confirm an objective response after the first post-treatment scan or up to 13 weeks, whichever occurred first. Interim analyses were completed and submitted to FDA on 05 Oct 2022, and FDA response was received on 09 Nov 2022. During this 21-week period (15 Jun 2022 to 09 Nov 2022), an additional 114 subjects were enrolled in the study, exceeding projected enrollment during this period of 60 subjects. Based on the number enrolled during this period, the estimated Part 1 total enrollment was updated in protocol amendment 4 to reflect these observed global enrollment rates at the time of the interim analysis (n=180). This change results in approximately 30 additional subjects being treated with the non-selected dose than projected in the original protocol. In addition, estimated enrollment in Part 2 was reduced (n=10) to ensure that 100 subjects in total would be enrolled at the selected dose.

***Does the FDA have further comments?***

**Discussion During Meeting:** FDA acknowledged Amgen's clarification. FDA then asked for further clarification regarding current enrollment in the two arms (i.e., the 10 mg and 100 mg dose levels) of Study 20200491 and specifically asked if Amgen was still enrolling patients to the 100 mg dose arm. Amgen replied that their team on this call was blinded to the trial data and that they did not know the exact number of patients enrolled to the 100 mg arm. Amgen clarified that they stopped enrolling patients to the 100 mg arm once they received FDA feedback regarding the selected dose for the trial.

**2. Summary of Clinical Safety and Summary of Clinical Efficacy**

Amgen plans to present the clinical safety and efficacy data from the phase 1 Study 20160323 and phase 2 registrational study 20200491 in the summary of clinical efficacy (SCE) and summary of clinical safety (SCS), respectively, to support the planned BLA for the proposed indication of the treatment of adult patients with (b) (4) SCLC with disease progression on or after (b) (4) lines of therapy.

**Does the agency agree with this approach?**

**FDA Response:** We do not object to your proposal regarding the efficacy data to be presented in the SCE. Refer to FDA response to Question 3 below regarding the pooled safety population to be included in the ISE and presented in the SCS.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's feedback and has no further comment.

**Discussion During Meeting:** Discussion did not occur during the meeting.

## Integrated Summaries

### 3. Integrated Summary of Safety

The Integrated Summary of Safety (ISS) will be submitted in Module 5, Section 5.3.5.3, and will consist of integrated summary data tables with no additional text. The SCS included in Module 2 will be sufficiently detailed to serve as the narrative portion for the ISS and will include hyperlinks to relevant components of the ISS in Module 5. Amgen will provide clear explanation of where all components of the ISS are located on Module 2 and Module 5.

Data will be pooled from the phase 1 Study 20160323 (tarlatamab monotherapy cohorts) and phase 2 Study 20200491. Detailed ISS proposal is presented in Section 4.1. The proposed ISS header is presented in Section 4.1.1.1.

**Does the agency agree with this proposal for the ISS?**

**FDA Response:** No. The pooled dataset for the ISS should include all patients across all studies who received tarlatamab as a single agent at the dose proposed for marketing (i.e., 10 mg dose). Data for patients who received lower or higher doses of tarlatamab, including the 100 mg dose, should not be pooled with data for the dose proposed for marketing. The ISS should present safety analyses for each separate study by dose level (Study 20160323 and Study 20200491) and for a pooled study population of patients who received tarlatamab at the 10 mg dose. While analyses from Study 20200491 for patients who received the dose proposed for marketing will be used for presentation of adverse events in Section 6 of the product labeling, analyses from the pooled safety population who received the dose proposed for marketing may be used to inform Section 5 (Warnings and Precautions).

In addition, please:

- Provide the estimated number of patients that would be included in each dose header in the ISS (i.e., 1→10 mg, and 1→100 mg)
- Update your threshold definition for TEAEs from 42 days from last dose of tarlatamab to 47 days given there is a (+5) day window at the safety follow-up visit from Study 20200491

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges FDA's feedback and agrees that pooled dataset for the ISS will

include all patients across all studies who received tarlatamab monotherapy at 10 mg dose.

Regarding FDA's comments "The ISS should present safety analyses for each separate study by dose level (Study 20160323 and Study 20200491) and for a pooled study population of patients who received tarlatamab at the 10 mg dose", Amgen proposes that the safety analyses for each separate study by dose level (Study 20160323 and Study 20200491) will be provided in the respective CSRs. A pooled study population of patients who received tarlatamab at the 10 mg dose will be provided in the ISS.

Study 20160323 includes 22 subjects at 1→10mg, and 63 subjects at 1→100mg.

In Parts 1 and 2 combined, Study 20200491 is estimated to enroll 100 subjects at 1→10mg and 90 subjects at 1→100mg.

Combining the two studies, it is estimated that there are 122 subjects at 1→10mg, and 153 subjects at 1→100mg.

Amgen will update the threshold definition for TEAEs from 42 days from last dose of tarlatamab to 47 days.

***Does the FDA have further comments?***

**Discussion During Meeting:** FDA stated that though Amgen's proposal to provide safety analyses for each separate study by dose level in the respective CSRs for Studies 20160323 and 20200491 appears reasonable, FDA reiterates their preliminary response that the ISS should present safety analyses for each separate study by dose level. FDA stated that the safety data to be presented in the ISS may comprise summary safety data for each dose level in each study while more detailed safety data may be provided in the respective CSRs.

**4. Adverse event (AE) Grading for Integrated Summary of Safety**

**Detailed AE grading proposal for ISS is presented in Section 4.1.4.**

**Does the agency agree with this approach?**

**FDA Response:** No. Please convert the CTCAE grading for all adverse events (AEs) to the most recent grading version between the two studies. In the BLA submission, please delineate which AEs were converted and the process used to convert all AEs. In addition, you should:

- Include in the ISS datasets side-by-side columns for AE term and Grade based on the different AE grading versions and columns showing AE term

and Grade before and after conversion. We recommend that you include a flag to identify in the datasets the AE terms and Grades that were changed and include in the submission a detailed description of the procedure used to convert the AE terms/Grades

- For any labeling that may be based on pooled safety analysis using different grading versions, include in the BLA submission a detailed summary and analysis of those adverse reactions and provide justification as to whether the change in grading version did/did not impact the safety profile of tarlatamab as described in the proposed labeling

Regarding the reporting of CRS, we strongly recommend that you use the most recent ASTCT criteria (Lee, 2019) to identify CRS events across both Studies 20160323 and 20200491. Please use the most recent CTCAE grading version to grade the preferred terms (PTs) used in defining CRS events across both Studies 20160323 and 20200491.

Regarding the reporting of neurological adverse events, including but not limited to ICANS, you may define ICANS based on the ASTCT criteria you reference in the meeting package (Lee, 2019). In addition, we strongly recommend that you also employ a broad search strategy that includes all adverse events under the MedDRA SOC of Psychiatric Disorders and Nervous System Disorders to identify the broad spectrum of neurological toxicities associated with tarlatamab across both Studies 20160323 and 20200491. You may present the summary of neurologic toxicity using both approaches side-by-side.

Regarding the grading of the preferred terms comprising the defined neurological events and syndromes based on either strategy, please use the most recent CTCAE grading version across both studies.

**Amgen's Response Received via Email on February 3, 2023:** Amgen agrees to convert CTCAE grading for all adverse events (AEs) in Study 20160323 from CTCAE v4.0 to CTCAE v5.0 using a mapping algorithm. In the BLA submission, Amgen will delineate which AEs were converted and the process used to convert all AEs. Amgen will also include the requested information in the bulleted points in FDA's response to Question 4.

In general, if all information is available for a subject who has an AE, we will map this AE from CTCAE v4.0 to v5.0. In case some information is missing, the AE will retain its originally assigned CTCAE v4.0 grade with a footnote to indicate that this original grading system has been used.

For example, for the PT hyperkalemia, grade 2 hyperkalemia definition was changed from CTCAE v4.0 to CTCAE v5.0. In CTCAE v4.0, grade 2 hyperkalemia is defined as >5.5 - 6.0 mmol/L. In CTCAE v5.0, grade 2 hyperkalemia is defined as >5.5 - 6.0 mmol/L; intervention initiated. In this

example, if we had all information available regarding the lab value of potassium and a description of the intervention, this AE would be mapped from CTCAE v4.0 to v5.0. However, if no information was given regarding details of intervention or does not mention whether there was an intervention, we would retain the CTCAE v4.0 grading.

Similarly, in CTCAE v4.0, grade 3 hyponatremia is defined as  $<130 - 120$  mmol/L. In CTCAE v5.0, grade 3 hyponatremia is defined as 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms. In this example, if we had all information available regarding the lab value of sodium and the symptoms, this AE would be mapped from CTCAE v4 to v5. However, if no information was given regarding details of symptoms, we would retain the CTCAE v4.0 grading.

For Cytokine Release Syndrome (CRS) adverse events, Amgen will adapt CRS events graded by Lee 2014 criteria in Study 20160323 to Lee 2019 criteria to facilitate comparison with Study 20200491. In general, if all information is available for a subject to assess the updated grading criteria, we will map this CRS event from Lee 2014 to Lee 2019 grading. In case that some information is missing, the CRS event will retain its originally assigned grade. To illustrate some differences in data collection for CRS between Lee 2014 and Lee 2019, eCRF collection forms for the respective studies are shown in the below table.

| <b>Study 20200491 eCRF<br/>(Based on Lee 2019)</b>   | <b>Study 20160323 eCRF<br/>(Based on Lee 2014)</b> |
|------------------------------------------------------|----------------------------------------------------|
| <b>Hypotension-IV Fluid Bolus</b>                    |                                                    |
| No IV fluid bolus                                    | IV Bolus                                           |
| IV fluid bolus                                       | No IV Bolus                                        |
| Unknown                                              |                                                    |
| <b>Hypotension-Vasopressors</b>                      |                                                    |
| No vasopressor                                       | 0 vasopressor                                      |
| Single vasopressor use (use including vasopressin)   | 1 vasopressor                                      |
| Multiple vasopressor use (not including vasopressin) | 2 vasopressors                                     |
| Unknown vasopressor use                              | 3 vasopressors                                     |
|                                                      | 4 vasopressors                                     |

|                                                                                     |                                                         |
|-------------------------------------------------------------------------------------|---------------------------------------------------------|
|                                                                                     | 5 vasopressors                                          |
| <b>Hypoxia-Supplemental Oxygen</b>                                                  |                                                         |
| No supplemental oxygen                                                              | No supplemental oxygen                                  |
| Low-flow $\leq 6$ L/min nasal cannula or blow-by                                    | Supplement oxygen $\leq 40\%$ with positive pressure    |
| High flow ( $> 6$ L/min) NC, facemask, non-rebreather mask, or Venturi mask         | Supplement oxygen $\geq 40\%$ with positive pressure    |
| Positive pressure ventilation (CPAP, BiPAP, intubation, and mechanical ventilation) | Supplement oxygen $\leq 40\%$ without positive pressure |
| Unknown supplemental oxygen                                                         | Supplement oxygen $\geq 40\%$ without positive pressure |

Two scenarios illustrating complexity with re-assigning grade from the 20160323 study are outlined here, with proposed solutions. These are not intended to represent an exhaustive list of limitations with CRS grade re-assignment but may serve as examples of our proposed guidelines during this process.

#### Organ toxicity defined CRS:

A CRS event for which Lee 2014 assigned grade is directly attributable to organ toxicity and is greater than what would be assigned by Lee 2019 criteria using only IV fluid, vasopressor or oxygen data will retain originally assigned grade, and be flagged in the listing as such. For example, a grade 3 event by 2014 criteria characterized by: no vasopressor, oxygen <40% FiO<sub>2</sub>, and grade 3 organ toxicity. While this scenario would be grade 2 by 2019 criteria, Amgen proposes this event retains grade 3, as originally assigned by investigator, with a flag in the listing to indicate a retained grade.

#### CRS events without associated treatments/interventions:

A CRS event on Study 20160323 for which Lee 2014 grading system is applied does not have eCRF notation of interventions or assessments leading to the assessment of grade. In the event that drivers of the grade are unable to be retrospectively determined, Amgen proposes that any such event will retain originally assigned grade and be flagged in the listing as such.

Amgen acknowledges FDA's feedback on defining ICANS based on the ASTCT criteria (Lee, 2019). Amgen will classify and grade all associated ICANS related neurological preferred terms across the studies using CTCAE version 5.0. In addition, the study 20200491 will include an additional preferred term of ICANS, graded by ASTCT Lee 2019. For the Study 20160323, there is no ICANS adverse event preferred term since this term did not exist in CTCAE v4.0.

#### ***Does the FDA agree with this plan?***

**Discussion During Meeting:** FDA stated that Amgen's proposed approach to converting grading of AE from CTCAE v4.0 to CTCAE v5.0, and CRS reporting based on the 2019 ASTCT criteria appears acceptable. FDA acknowledged Amgen's point that ICANS was a preferred term in Study 20200491 based on CTCAE v.5 but not in Study 20160323 since ICANS was not a preferred term in CTCAE v4.0 that was used for safety reporting in Study 20160323. FDA stated that this is an additional reason to support FDA's recommendation that Amgen also employ the alternative broader search strategy for neurological toxicities that will be comparable for both Studies 20160323 and 20200491. FDA added that Amgen should have a charter outlining their strategy for mapping and conversion of AEs and CRS to the most recent versions.

## **5. Integrated Summary of Efficacy**

**An Integrated Summary of Efficacy (ISE) analysis is not planned for the BLA filing. Detailed rationale for the proposal is presented in Section 4.2.**

**Does the agency agree with this approach?**

**FDA Response:** No. An Integrated Summary of Efficacy (ISE) should be included in the planned BLA submission. While pooling of efficacy data across studies is not required or recommended, the ISE should contain an integrated description of efficacy across all settings that can help inform an assessment of the efficacy of a new drug.

As outlined in in *FDA's Guidance for Industry - Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document* (available at: <https://www.fda.gov/media/75783/download>), there may be situations in which section 2.7.3, Summary of Clinical Efficacy (SCE) would be sufficiently detailed to serve as the narrative portion of the ISE while still concise enough to meet the suggested size limitations for Module 2. This situation is rare but can occur if an application is small and consists of a single study or a number of small studies. In such situations, the ISE can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 and the appendices of tables, figures, and datasets located in Module 5. If the ISE is split across modules in this way, it is critical to include a clear explanation of where all components are located. This explanation should be placed in Module 2 (section 2.7.3) and in Module 5 (section 5.3.5.3).

**Amgen's Response Received via Email on February 3, 2023:** Efficacy results from pivotal phase 2 Study 20200491 on tarlatamab monotherapy in subjects with SCLC will be presented as the primary support for the proposed indication and will not be pooled with efficacy data from any other ongoing tarlatamab monotherapy or combination studies. A brief summary of phase 1 data from Study 20160323 on tarlatamab monotherapy in previously treated subjects with SCLC will be included as supportive data.

Amgen does not intend to include efficacy data from the following studies in the planned BLA:



- Study 2021004 phase 3 second-line SCLC confirmatory RCT

Given the amount of efficacy data from the two studies noted above which will be included in the BLA, Amgen maintains that the SCE can be written to include all necessary data tables and a sufficiently detailed narrative while still remaining concise enough to meet the suggested size limitations of Module 2. Therefore, Amgen proposes to not include a separate ISE.

**Does the Agency agree?**

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Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

**Discussion During Meeting:** FDA stated that they did not agree with Amgen's proposal to not submit an ISE. FDA stated that an ISE should be included in the original BLA. FDA also stated that they agree that efficacy data should not be pooled across studies. FDA added that the ISE should include all efficacy data from all completed studies of tarlatamab across tumor types and any available data from ongoing studies across tumor types, but does not need to include data from ongoing randomized studies. FDA stated that such data is considered supportive data in the assessment of efficacy. FDA added that the ISE should include a brief presentation of topline results from such studies.

## 6. Integrated Summary of Immunogenicity

**Detailed rationale for the integrated summary of immunogenicity (ISI) proposal is presented in Section 4.3.**

**Does the agency agree with this proposal for the ISI?**

**FDA Response:** No, we do not agree with your proposal to not provide a standalone Integrated Summary of Immunogenicity in section 5.3.5.3 of the BLA. For tracking purposes, and consistency with guidance for industry *Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection*, section 5.3.5.3 of the BLA should include a standalone Integrated Summary of Immunogenicity. Your plan to provide a summary of the immunogenicity results in relevant places in section 2.7 is acceptable; include references and links to the Integrated Summary of Immunogenicity in Section 2.7 as appropriate.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's recommendation and will provide a standalone ISI in section 5.3.5.3.

**Discussion During Meeting:** Discussion did not occur during the meeting.

## Subject Narratives and Case Report Forms

### 7. Subject Narratives

**Amgen proposes to submit subject safety narratives for deaths, adverse events (serious and non-serious) resulting in study discontinuation or permanent discontinuation of study treatment, serious adverse events (SAEs), and selected adverse events of interest (see Section 5.1).**

**Does the agency agree with this proposal?**

**FDA Response:** Your proposal is generally acceptable. However, please clarify the selected adverse events of interest for which you plan to provide narratives.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges FDA's comments and clarifies the following events of interest for which Amgen would provide narratives:

Neutropenia – Narratives would include all adverse events and serious adverse events identified using the Amgen MedDRA Query (AMQ) of neutropenia (broad). This will not include events from laboratory findings.

Cytokine release syndrome (CRS) – Narratives would include all adverse events and serious adverse events identified using the AMQ of CRS (broad).

An Amgen MedDRA Query (AMQ) for Neutropenia and CRS has been created to include preferred terms to be used in tarlatamab studies and is included in Appendix 1.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) - Narratives would include all adverse events and serious adverse events identified using the AMQ of ICANS (broad) and the System Organ Class (SOC) of Psychiatric Disorders and Nervous System Disorders. Please refer to Appendix 4 -Meeting Background Materials SN 0116.

***Does the FDA have further comments on this?***

**Discussion During Meeting:** FDA stated that Amgen's proposed selected adverse events of interest appear reasonable.

## **8. Hyperlinked Case Report Forms**

**Amgen proposes to provide case report forms (CRFs) with hyperlinked queries from Study 20160323 and 20200491 for all serious adverse events including deaths and adverse events (serious and non-serious) leading to discontinuation of tarlatamab (see Section 5.2).**

**Does the agency agree with this proposal?**

**FDA Response:** Yes.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's feedback and has no further comment.

**Discussion During Meeting:** Discussion did not occur during the meeting.

## 90-Day Updates

### 9. 90-Day Safety and Efficacy Update

Amgen proposes to submit a 90-day safety update report to provide the updated safety data. Detailed proposal is presented in Section 6.

- a. Does the agency agree with the submission of 90-day safety update report with the proposed additional months of safety data?

**FDA Response:** Yes.

- b. Does the agency agree with the proposal regarding submission of the updated efficacy data with the 90-day safety update report and that submission of the updated efficacy data will not impact the BLA review timeline and the PDUFA action date?

Does the FDA agree with the proposed content and analysis for the 90-day safety update?

**FDA Response:** While it would be acceptable to provide updated efficacy data in the 90-day safety update report, previous assessments of response should not be re-adjudicated. This means that ORR results should not change unless a new response occurred after the original data cut-off date and updated duration of response for responses documented prior to the original cut-off date should be based on date of response used for the initial BLA submission.

In general, submission of updated efficacy data with the 90-safety update report alone would not be expected to impact the PDUFA action date.

The proposed content and analyses for the 90-day safety update appears acceptable. In addition, please clarify if safety narratives for other ongoing studies [REDACTED] (b) (4) that will not be provided at the initial BLA filing will be provided as part of the 90-day safety update.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's comment and clarifies the narrative plan below.

Initial BLA submission will include the following:

- Study 2016323 and Study 20200491: Narratives for serious adverse events, including deaths, adverse events (serious and nonserious events) leading to treatment or study discontinuation and adverse events of interest as defined in 7.1.1 of this response.

- [REDACTED] (b) (4)

90-day safety update will include the following:

- Study 2016323 and Study 20200491: New safety narratives and updates to previously submitted narratives for all serious adverse events, including deaths, and for all adverse events (serious and nonserious events), leading to treatment discontinuation and all subjects with an adverse event of interest from the data cut-off used for initial BLA submission through the data cut-off for the 90-day safety update.

Safety narratives for other studies [REDACTED] (b) (4)  
[REDACTED] will not be provided as part of 90-day safety update.

***Does the FDA agree with this proposal?***

**Discussion During Meeting:** FDA stated that Amgen's proposed approach to submission of case narratives appears reasonable.

### **Modified Monitoring Safety Cohort**

#### **10. Data Presentation of Part 3: Modified Monitoring Safety Cohort**

**Data presentation proposal for modified monitoring safety cohort is presented in Section 7.**

**Does the FDA agree with the proposed data presentation for the modified monitoring safety cohort?**

**FDA Response:** Your proposal to submit safety data for the modified monitoring safety cohort appears acceptable. Since patients in this modified monitoring safety cohort will be treated at the dose proposed for marketing (i.e., the 10 mg dose), it may be acceptable to pool the safety data for this cohort with the safety data for patients in Parts 1 and 2 treated with the 10 mg dose in Study 20200491. However, you should also present the safety data for this modified monitoring safety cohort side-by-side with the safety data from Parts 1 and 2.

In addition, you should also provide the efficacy data for this cohort in the initial BLA submission and in the 90-day safety update. You may provide the efficacy data for the modified monitoring safety cohorts separate from the efficacy data for patients included in the primary efficacy population from Parts 1 and 2 of Study 20200491. If at the time of the 90-day safety update the follow-up for this modified monitoring safety cohort is long enough based on the recommendations we have provided in our response to Question 1, during our review we may

consider pooling this efficacy data with the primary efficacy data from Parts 1 and 2.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's recommendations for Part 3 (Modified Monitoring Cohort). Amgen plans to present Part 3 safety data side-by-side with safety data from Parts 1 and 2 and to pool the safety data for this cohort with the safety data for patients in Parts 1 and 2 treated with the 10 mg dose in Study 20200491. Amgen will include efficacy data for Part 3 in the initial BLA submission and in the 90-day safety update. These data will be presented separately from the primary efficacy population, which is defined by Parts 1 and 2 of Study 20200491.

**Discussion During Meeting:** Discussion did not occur during the meeting.

## Data Standardization Plan

### 11. SDTM and ADaM Datasets

In the planned BLA, Amgen proposes to follow the Guidance for Industry Providing Regulatory Submissions in Electronic Format – Standardized Study Data, specified in the “Study Data Technical Conformance Guide” (v5.0 October 2022) to the best extent possible.

Amgen will provide tabulation datasets in the Clinical Data Interchange Standards Consortium (CDISC) format with SDTM v1.4 / SDTM-IG v3.2 and ADaM v2.1 / ADaM-IG v1.2. Amgen proposes to submit Define-XML v2.0 for SDTMs and Define-XML v2.0 ADaMs for Studies 20160323, 20200491 and ISS.

For Studies 20160323 and 20200491, Amgen proposes to include analysis result metadata (ARM) for primary and key secondary endpoint tables that indicate which ADaM dataset variables and sample codes were used to produce these tables. Analysis result metadata will take the format of annotated tables. For Studies 20160323 and 20200491, Amgen proposes to include non-executable SAS programs for primary and key secondary endpoint tables.

Details of the analysis for which SDTM and ADaM datasets are described in Section 8.1. A detailed description of the data package in a Study Data Standardization Plan (SDSP) is provided in Appendix 1.

**Does the agency agree with this proposal?**

**FDA Response:** The proposal appears acceptable. However, a final determination will be made during the filing review of the BLA submission.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's feedback and has no further comment.

**Discussion During Meeting:** Discussion did not occur during the meeting.

**12. Clinical Pharmacology NONMEM Datasets for PK and exposure-response Analysis**

**Data presentation proposal for population PK and exposure-response analysis is presented in Section 8.2.**

**Does the agency agree with this proposal?**

**FDA Response:** The proposal generally appears acceptable. PK data from other studies could also be included to increase model robustness if needed. A final determination will be made after reviewing the data during review of the BLA. Refer to Question 4 regarding the pooling approach for key safety variables.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's feedback.

**Discussion During Meeting:** Discussion did not occur during the meeting.

**13. Bioresearch Monitoring (BIMO)**

**Amgen proposes to provide the general study information and the CLINSITE dataset only for sites that participated in Study 20200491. Site-specific efficacy results will be produced only for Study 20200491 subjects and will follow the specifications outlined in FDA's document titled "FDA Bioresearch Monitoring Technical Conformance Guide" version 3.0.**

**Does the agency agree with this proposal?**

**FDA Response:** Yes. Your proposal to provide general study information and the CLINSITE dataset only for sites that participated in Study 20200491 is acceptable.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's feedback and has no further comment.

**Discussion During Meeting:** Discussion did not occur during the meeting.

**14. Study 20160323 and 20200491 ADaM datasets: ADEVENT**

Amgen proposes to create an Intermediate dataset called ADEVENT (Tumor Response Event Date Analysis Data). ADEVENT will aid review and traceability when creating the ADTTE (Time to Event Analysis) dataset. The variable PARQUAL will be used to separate the investigator and independent assessor results. For the mock submission, only investigator assessments will currently be included in the ADEVENT and ADTTE datasets, so their structure may change.

**Does the agency agree with this proposal?**

**FDA Response:** The proposal appears acceptable. However, we may send information requests during the review cycle as deemed necessary.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's feedback and has no further comment.

**Discussion During Meeting:** Discussion did not occur during the meeting.

**eCTD Content and Structure for the Planned BLA**

**15. BLA Structure and Content**

The proposed table of contents for Module 1 through Module 5 for the planned BLA is provided in Appendix 2 (see Section 9).

**Does the agency agree that the proposed eCTD content and structure is adequate to support a BLA for the proposed indication under the accelerated approval pathway?**

**FDA Response:** The proposed eCTD content and structure is acceptable to support a BLA submission with the exception to include an ISE and ISI; please see FDA comments to questions 5 and 6.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's feedback and has no further comment.

**Discussion During Meeting:** Discussion did not occur during the meeting.

**ADDITIONAL FDA COMMENT****Clinical**

16. At the time of a BLA submission intended to support the accelerated approval of tarlatamab, the proposed confirmatory trial intended to verify the clinical benefit of tarlatamab should be well underway. If the confirmatory trial is not well underway, submission of a BLA seeking accelerated approval may not be considered appropriate. At the time of the pre-BLA meeting, please provide an update on the enrollment status of Study 20210004, which you have previously indicated you intend to use to verify the clinical benefit of tarlatamab.

**Amgen's Response Received via Email on February 3, 2023:** Amgen acknowledges the FDA's feedback and will provide an update on the enrollment status of Study 20210004 (planned confirmatory trial) at the time of the pre-BLA meeting.

**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) 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 draft 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](https://www.fda.gov).<sup>2</sup>

## **FDARA REQUIREMENTS**

Sponsors 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.

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<sup>2</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at [OCEPERC@fda.hhs.gov](mailto:OCEPERC@fda.hhs.gov). For further guidance on pediatric product development, please refer to FDA.gov.<sup>3</sup>

### **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](mailto: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).

### **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, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR<sup>4</sup>: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid<sup>5</sup>

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<sup>3</sup> <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

<sup>4</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

<sup>5</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

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/s/  
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IND 134859

**MEETING MINUTES**

Amgen Inc.  
Attention: Sunyoung Lee, MS, PhD  
Director, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop: 27-2-D  
Thousand Oaks, CA 91320

Dear Dr. Lee:<sup>1</sup>

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tarlatamab.

We also refer to the video conference between representatives of your firm and the FDA on December 5, 2022. The purpose of the meeting was to discuss the study design of the proposed Phase 3 clinical trial, Study 20210004, including the endpoints, (b) (4), to support full approval of the proposed second-line indication. You also requested feedback on the combination dose selection for the expansion phase of the first-line Phase 1b trial, Study 20200469.

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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<sup>1</sup> 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](mailto:Ashley.Lane@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Ashley Lane, MS  
Consumer Safety Officer  
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



## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-Phase 3

**Meeting Date and Time:** December 5, 2022; 3:00 PM – 4:00 PM, EST  
**Meeting Location:** Teleconference

**Application Number:** IND 134859  
**Product Name:** Tarlatamab  
**Indication:** Small cell lung cancer  
**Sponsor Name:** Amgen Inc.  
**Regulatory Pathway:** 351(a) of the Public Health Service Act

**Meeting Chair:** Nicole Drezner  
**Meeting Recorder:** Ashley Lane

### CDER Participants:

Erin Larkins, Acting Supervisory Associate Director, Division of Oncology 2 (DO2)  
Nicole Drezner, Cross Disciplinary Team Lead, DO2  
Oladimeji Akinboro, Clinical Reviewer, DO2  
Jeanne Fourie Zirkelbach, Clinical Pharmacology Team Leader, Division of Cancer Pharmacology II (DCP II)  
Lingshan Wang, Clinical Pharmacology Reviewer, DCP II  
Anup Amatya, Acting Biostatistics Team Leader, Division of Biometrics V (DBV)  
Yi Ren, Biostatistics Reviewer, DBV  
Erica Horodniceanu, Health Scientist, Oncology Center of Excellence  
Ashley Lane, Consumer Safety Officer, DRO

### SPONSOR ATTENDEES

Brian Abbott, Director, Regulatory Affairs  
Gwyn Bebb, MD, PhD, Medical Director, Clinical Research  
Giuseppe Giaccone, MD, PhD, Vice President, Global Development  
Danielle Jandial, MD, Executive Medical Director, Global Development  
Brett Houk, Director, Clinical Pharmacology  
Jackie Kline, PhD, Vice President, Regulatory Affairs  
Sunyoung Lee, PhD, MS, Director, Regulatory Affairs  
Claudia Arredondo Pimentel, Senior Manager, Regulatory Affairs  
Mukul Minocha, PhD, Senior Principal Scientist, Clinical Pharmacology  
Sujoy Mukherjee, MD, Medical Director, Global Patient Safety  
Ramachandran Suresh, PhD, Executive Director, Biostatistics  
Gaurav Suri, MSc, Director, Health Economics  
Alicia Zhang, PhD, Director, Biostatistics

## BACKGROUND

### Meeting Purpose

On September 23, 2022, FDA received a Type B meeting request from Amgen to discuss the study design of the proposed randomized clinical trial, Study 20210004, including the endpoints, (b) (4) to support full approval of the proposed second-line indication. Amgen is also seeking feedback on the combination dose selection for the expansion phase of the first-line Phase 1b study, Study 20200469.

FDA sent Preliminary Comments to Amgen on November 29, 2022.

### Regulatory

FDA granted Orphan Drug designation to tarlatamab for the treatment of small cell lung cancer (SCLC) on December 27, 2018.

### Clinical Pharmacology

On October 5, 2022, Amgen submitted clinical data from Studies 20160323 and 20200491, described below, to support the proposed 10 mg dose of tarlatamab for further evaluation in registration-enabling trials for FDA review and concurrence.

#### *Study 20160323: First-in-human (FIH) dose escalation study*

As of July 2022, 181 patients with SCLC were enrolled, 176 of whom received at least one dose of tarlatamab. Patients were administered tarlatamab intravenously (IV) every 2 weeks (Q2W), at doses ranging from 0.003 to 100 mg.

Exposure-response analyses conducted by Amgen showed a significant exposure-response relationship for confirmed or unconfirmed ORR versus average concentration (C<sub>avg</sub>) across the doses studied. Based on the safety profile and the incremental benefit of the 10 mg and 100 mg doses over the lower doses studied, the 10 mg and 100 mg doses were chosen to move forward in Study 20200491.

#### *Study 20200491: Dose randomization and dose expansion study*

Study 20200491 evaluated the efficacy, safety, tolerability, and pharmacokinetics (PK) of tarlatamab in patients with relapsed/refractory SCLC with progression after one platinum-based regimen and at least one other line of therapy. In Part 1, patients were randomized to receive either 10 mg or 100 mg of tarlatamab IV Q2W. A pre-specified interim analysis was conducted to select one of the two doses for further evaluation after 30 patients in each arm had received at least one dose of tarlatamab and had the opportunity to have tumor response confirmed. Part 2 was designed to further evaluate tarlatamab at the selected dose level.

*Exposure-Response Analyses from Studies 20160323 and Studies 20200491*

Exposure-efficacy analyses based on Part 1 of Study 20200491 (N = 62) showed that the relationship between exposure and disease control rate (DCR) and objective response rate (ORR) was not significant. However, the exposure-efficacy analyses for the combined dataset from Studies 20160323 and 20200491 (N = 220) showed a significant relationship between exposure and ORR/DCR (Table 1).

**Table 1. Exposure-response model predicted probability (95%CI) of achieving response criteria at the selected tarlatamab target doses**

| Model predicted metrics      | Part 1 Phase 2<br>(n=62) |                  | FIH and Part 1 Phase 2<br>(n=220) |                  |
|------------------------------|--------------------------|------------------|-----------------------------------|------------------|
|                              | 10 mg                    | 100 mg           | 10 mg                             | 100 mg           |
| Confirmed objective response | 32%<br>(21 – 46)         | 43%<br>(28 – 61) | 24%<br>(19 – 31)                  | 33%<br>(26 – 42) |
| Disease control rate         | 67%<br>(53 – 78)         | 80%<br>(63 – 90) | 53%<br>(46 – 60)                  | 66%<br>(57 – 73) |

Confirmed ORR requires 2 consecutive scans with PR or CR

Disease control rate includes stable disease, complete response and partial response

Source: Module 1.11.3—Clinical Information Amendment: Rationale for Recommended Phase 2 Dose, SDN 438, pg 69.

Exposure-response analyses were also conducted for the key safety endpoints of neutropenia, cytokine release syndrome (CRS), and neurological events using data from the 125 evaluable patients from Part 1 of Study 20200491. The predicted mean probability of occurrence of Grade  $\geq 2$  and Grade  $\geq 3$  key safety events in patients with SCLC at the median exposures associated with selected target doses are shown in Table 2. These analyses demonstrated that increasing tarlatamab exposures were associated with higher incidences of Grade  $\geq 3$  CRS and Grade  $\geq 2$  or Grade  $\geq 3$  neurological events, although the relationship was not statistically significant.

**Table 2. Exposure-safety model predicted probability (95%CI) of occurrence of key safety events at the selected target doses**

| Adverse Event | ≥ Grade 2     |               | ≥ Grade 3    |               |
|---------------|---------------|---------------|--------------|---------------|
|               | 10 mg (n=44)  | 100 mg (n=42) | 10 mg (n=44) | 100 mg (n=42) |
| CRS           | 25% (16 – 36) | 23% (13 – 38) | 2% (0 – 13)  | 11% (4 – 25)  |
| Neutropenia   | 4% (1 – 13)   | 6% (2 – 18)   | 0% (0 – 100) | 2% (0 – 23)   |
| Neurotoxicity | 21% (13 – 33) | 31% (19 – 46) | 1% (0 – 14)  | 12% (5 – 27)  |

Maximum grade within a subject was assessed

n=86 for subjects with both PK and efficacy measures

Source: Module 1.11.3—Clinical Information Amendment: Rationale for Recommended Phase 2 Dose, SDN 438, pg 71.

Based on the exposure-response analysis, a tarlatamab target dose of 10 mg (with a step dose of 1 mg on treatment initiation) was chosen to balance the efficacy/safety of tarlatamab in patients with SCLC. FDA communicated to Amgen via email on November 9, 2022, that the 10 mg dose appears acceptable as the dose for continued study in Part 2 of Study 20200491 and for further evaluation for Phase 2 and Phase 3 trials in patients with relapsed/refractory SCLC.

## Clinical

*Proposed Study 20210004: study intended to support a marketing application*

Amgen proposes a randomized, open-label, international, multi-center trial comparing the efficacy of tarlatamab as a single agent to standard of care (SoC) therapy for the treatment of patients with relapsed (b) (4) SCLC who have experienced disease progression after receiving one prior line of platinum-based therapy. (b) (4)

(b) (4)

(b) (4)

## **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) 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 draft 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](https://www.fda.gov).<sup>2</sup>

## **FDARA REQUIREMENTS**

Sponsors 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

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<sup>2</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

Manager by email at [OCEPERC@fda.hhs.gov](mailto:OCEPERC@fda.hhs.gov). For further guidance on pediatric product development, please refer to FDA.gov.<sup>3</sup>

## **DATA STANDARDS FOR STUDIES**

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.<sup>4</sup>

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team ([cdeler-edata@fda.hhs.gov](mailto:cdeler-edata@fda.hhs.gov)) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page<sup>5</sup> that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in

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<sup>3</sup> <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

<sup>4</sup> <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

<sup>5</sup> <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at [FDA.gov](https://www.fda.gov). For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.3 eCTD Sample Submission pg. 44) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at [FDA.gov](https://www.fda.gov).<sup>6</sup>

## **DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS**

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

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<sup>6</sup> <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

### **LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources<sup>7</sup>.

### **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

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<sup>7</sup> <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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](mailto: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).

### **OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those 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). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.<sup>8</sup>

### **NEW PROTOCOLS AND CHANGES TO PROTOCOLS**

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

- (1) Study phase
- (2) Statement of whether the study is intended to support marketing and/or labeling

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<sup>8</sup> <https://www.fda.gov/media/85061/download>

changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

### **UNITED STATES PATIENT POPULATION**

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

### **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, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR<sup>9</sup>: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid<sup>10</sup>

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<sup>9</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

<sup>10</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

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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.**  
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/s/  
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ASHLEY R LANE  
12/07/2022 05:36:38 PM



IND 134859

**MEETING MINUTES**

Amgen, Inc.  
Attention: Sunyoung Lee, M.S., Ph.D.  
Manager, Regulatory Affairs  
1 Amgen Center  
Thousand Oaks, CA 91320

Dear Dr. Lee:

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 teleconference between representatives of your firm and the FDA on September 14, 2020. The purpose of the teleconference was to discuss the clinical development program for AMG 757 (b) (4) for the second line treatment of small cell lung cancer (SCLC) (b) (4).

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the teleconference outcomes.

If you have any questions, please call me at 301-796-2320 or email [sharon.sickafuse@fda.hhs.gov](mailto:sharon.sickafuse@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Sharon Sickafuse, M.S.  
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

Enclosure:

- Teleconference Minutes



## MEMORANDUM OF TELECONFERENCE MINUTES

**Meeting Type:** Type B(EOP)  
**Meeting Category:** EOP2/PP3  
**Teleconference Date:** September 14, 2020

**Application Number:** IND 134859  
**Product Name:** AMG 757  
**Indications:**

(b) (4)

AMG 757 for the treatment of patients with (b) (4) SCLC  
with disease progression on or after platinum-based  
therapy (b) (4)

**Sponsor Name:** Amgen, Inc.  
**Regulatory Pathway:** 351(a) of the Public Health Service Act

**Meeting Chair:** Nicole Drezner  
**Meeting Recorder:** Sharon Sickafuse

### FDA ATTENDEES

#### Office of Oncologic Diseases

Katie Chon, PharmD  
Nicole Drezner, M.D.  
Dickran (Diko) Kazandjian, M.D.  
Janice Kim, PharmD  
Abigal (Abby) Koch, M.D.  
Harpreet Singh, M.D.

#### Office of Biostatistics

Division V  
Somak Chatterjee, Ph.D.  
Pallavi Mishra-Kalyani, Ph.D.

#### Office of Clinical Pharmacology

Division of Cancer Pharmacology II  
Meng Li, Ph.D.  
Hong Zhao, Ph.D.

**Office of Regulatory Operations**

Division of Regulatory Operations – Oncologic Diseases for DO2

Emily Pak, PharmD

Sharon Sickafuse, M.S.

**SPONSOR ATTENDEES**

Greg Friberg, M.D., Vice President, Global Development, Clinical

Danielle Jandial, M.D., Medical Director, Global Development

Nooshin Hashemi Sadraei, M.D. Medical Director, Early Development

Amy Xia, Ph.D., Vice President, Global Development, Biostatistics

Ramachandran Suresh, Ph.D., Executive Director, Biostatistics

Matthew Gribbin, Ph.D., Director, Biostatistics

Hui Yang, Ph.D., Senior Manager, Biostatistics

Sujoy Mukherjee, M.D., Medical Director, Global Safety

Mark Salvati Global Product General Manager

Julie Lepin, Ph.D., Vice President, Regulatory Affairs

Jackie Kline, Ph.D., Executive Director, Regulatory Affairs

Brian Abbott, Ph.D., Director, Regulatory Affairs

Sunyoung Lee, Ph.D., M.S., Manager, Regulatory Affairs

**BACKGROUND**

On June 19, 2020, Amgen submitted a meeting request (SDN 80) to discuss the clinical development program for (b) (4)

**Regulatory**

FDA granted Orphan Drug designation to AMG 757 for the treatment of SCLC on December 27, 2018.

**Clinical and Statistical**

AMG 757 is a bispecific T cell engager (BiTE) that targets DLL3 and CD3 under development for the treatment of SCLC for the following proposed indications:

| Line of therapy | Indication | Study names |
|-----------------|------------|-------------|
| (b) (4)         |            |             |



U.S. Food and Drug Administration

Silver Spring, MD 20993

[www.fda.gov](http://www.fda.gov)

|         |                                                                                                        |                                             |
|---------|--------------------------------------------------------------------------------------------------------|---------------------------------------------|
|         |                                                                                                        | (b) (4)                                     |
| (b) (4) | For the treatment of patients with disease progression on or after platinum-based chemotherapy (b) (4) | Study 20160323 (phase 2 portion)<br>(b) (4) |

Study 20160323 (ongoing)

Study 20160323 is an ongoing, first-in-human, ascending, multiple dose study of AMG 757 in patients with SCLC being conducted in three parts:

- Part A: dose exploration (Part A1) and expansion (Part A2) study in patients with relapsed/refractory SCLC who have progressed after at least one prior platinum-based chemotherapy regimen
- Part B: to commence when the MTD/RP2D of AMG 757 is established in Part A in patients with ED-SCLC with ongoing clinical benefit after no more than 6 cycles of platinum-based chemotherapy
- Part C: to evaluate the safety/tolerability and estimate the MTD/RP2D of AMG 757 in combination with pembrolizumab in patients with relapsed/refractory SCLC.

As of January 22, 2020, preliminary safety data are available for 30 patients enrolled in Part A1 and the most common ( $\geq 20\%$ ) adverse events reported include cytokine release syndrome (37%), pyrexia (27%), anemia, fatigue, and nausea (23% each), and headache (20%). As of April 21, 2020, preliminary efficacy data show a confirmed partial response (PR) in 4 patients (13%). At the time of this submission, a RP2D has *not* been determined.

Once the RP2D is determined, Amgen proposes to add a phase 2 dose expansion portion to the study and include 100 patients with relapsed/recurrent SCLC who have progressed on one platinum-based regimen (with or without an anti-PD-1/L1 agent). The primary objective is to determine the RECIST 1.1 overall response rate (ORR) based on BICR of AMG 757.

(b) (4)

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(b) (4)

### Clinical Pharmacology

12. *Does the Agency agree that the proposed clinical pharmacology package would support the planned submission(s) of AMG 757 for the treatment of subjects with SCLC?*

FDA Response:

FDA has no objection to Amgen's proposed approach of population PK and exposure-response analyses. Refer to FDA Guidance for Industry "Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications" available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072109.pdf> and "Population Pharmacokinetics" available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072137.pdf> for additional guidance.

Discussion:

Amgen did not have any questions or comments.

13. *Does the Agency agree that based on the mechanism of action, a thorough-QT study is not required for AMG 757?*

FDA Response:

FDA agrees that a thorough-QT study is not required for AMG 757.

Discussion:

Amgen did not have any questions or comments.

**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 this meeting. 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 draft 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](https://www.fda.gov).<sup>1</sup>

## **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](mailto:OCEPERC@fda.hhs.gov). For further guidance on pediatric product development, please refer to [FDA.gov](https://www.fda.gov).<sup>2</sup>

## **DATA STANDARDS FOR STUDIES**

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.<sup>3</sup>

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<sup>1</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

<sup>2</sup> <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

<sup>3</sup> <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team ([cdereadata@fda.hhs.gov](mailto:cdereadata@fda.hhs.gov)) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page<sup>4</sup> that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at [FDA.gov](http://fda.gov). For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

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<sup>4</sup> <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.<sup>5</sup>

### **LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources<sup>6</sup> and the CDER/CBER Position on Use of SI Units for Lab Tests website.<sup>7</sup>

### **NEW PROTOCOLS AND CHANGES TO PROTOCOLS**

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling

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<sup>5</sup> <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

<sup>6</sup> <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

<sup>7</sup> <https://www.fda.gov/media/109533/download>

changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

### **UNITED STATES PATIENT POPULATION**

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

### **ATTACHMENT**

Amgen's presentation

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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.**  
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/s/  
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SHARON K SICKAFUSE  
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