BLA 761344

BLA ACCELERATED APPROVAL

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

Dear Claudia Arredondo Pimentel:

Please refer to your biologics license application (BLA), dated and received October 12, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for IMDELLTRA (tarlatamab-dlle) injection, for intravenous use.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 1080 to Amgen Inc., Thousand Oaks, California, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product IMDELLTRA (tarlatamab-dlle). IMDELLTRA is indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture tarlatamab-dlle drug substance at (b) (4) The final formulated drug product will be manufactured and filled at Amgen Inc. in Thousand Oaks, California, and labeled and packaged at Amgen Manufacturing Ltd, Juncos, Puerto Rico. The IV Solution Stabilizer will be manufactured and filled at Amgen Technology (Ireland) Unlimited Company in Dun Laoghaire, Ireland, and labeled and packaged at Amgen Manufacturing Ltd, Juncos, Puerto Rico. You may label your product with the proprietary name, IMDELLTRA, and market it in 1 mg and 10 mg lyophilized powder in single-dose vials for reconstitution and further dilution for intravenous infusion.

DATING PERIOD

The dating period for IMDELLTRA shall be 30 months from the date of manufacture when stored at 2°C to 8°C, protected from light. The dating period for IV Solution Stabilizer shall be 60 months from the date of manufacture when stored at 2°C to 8°C, protected from light. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

The expiration date for the packaged product, IMDELLTRA (tarlatamab-dlle) plus IV Solution Stabilizer shall be dependent on the shortest expiration date of any component.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of IMDELLTRA and each kit component to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of IMDELLTRA, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 601.41, effective on the date of this letter, for use as recommended in the enclosed agreed-upon approved labeling. This BLA provides for the use of IMDELLTRA for the treatment of adult patients with ES-SCLC with disease progression on or after platinum-based chemotherapy.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in the draft guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* (October 2009).[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your May 13, 2024, submission containing final printed carton and container labeling.

ADVISORY COMMITTEE

Your application for IMDELLTRA was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trial(s) with due diligence. If required postmarketing clinical trial(s) fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement(s) specified in your submission dated May 6, 2024. This requirement is listed below.

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

The timetable you submitted on May 6, 2024, states that you will conduct this study/trial according to the following schedule:

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

[2] When final, this guidance will represent FDA's current thinking on this topic. 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.

Final Protocol Submission: 12/2022 (Completed)
Trial Completion: 04/2026
Final Report Submission: 08/2026

Submit clinical protocols to your IND 134859 for this product. FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this BLA 180 days after the date of approval of this BLA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted[3].

Your 180-day reports must include the information listed in 21 CFR 601.70(b). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**BLA 761344 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this BLA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.
[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and neurologic toxicity.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

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

Subjects with Relapsed Small Cell Lung Cancer After Platinum-based First-line Chemotherapy (DeLLphi-304)".

The timetable you submitted on May 6, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Analysis Plan):	01/2025
Final Protocol Submission (Analysis Plan):	04/2025
Trial Completion:	04/2026
Final Report Submission:	08/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

Submit clinical protocol(s) to your IND 134859 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4635-3 Conduct an integrated analysis from ongoing, completed, or planned clinical trials and other potential data sources as appropriate enrolling a sufficient representation of United States (U.S.) racial and ethnic minority patients that is reflective of the U.S. population of patients with SCLC, to further characterize the efficacy, safety and pharmacokinetics of tarlatamab in these patients. In the analysis, include a sufficient number of patients enrolled in the U.S. and a sufficient number of racial and ethnic minority patients reflective of the incidence of SCLC in each subpopulation to allow for interpretation of the results. The analyses should support comparative efficacy and safety outcome analyses between the aforementioned populations and White patients.

The timetable you submitted on May 6, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Analysis Plan):	01/2025
Final Protocol Submission (Analysis Plan):	04/2025
Trial Completion:	10/2026
Final Report Submission:	04/2027

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

POSTMARKETING COMMITMENT NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4635-4 To develop a Monocyte Activation Test (MAT) for reliable endotoxin detection of the IV Solution Stabilizer (IVSS). The method feasibility study results will be submitted to the Agency by January 2025. If the method feasibility study is successful, method validation with three batches of IVSS product will be submitted by January 2026. If the MAT method proves infeasible, Amgen commits to develop an alternative endotoxin detection method which is not subject to low endotoxin recovery for the IVSS and to provide a timeline for those studies.

The timetable you submitted on February 1, 2024, states that you will conduct this study according to the following schedule:

Feasibility Study:	01/2025

Final Report Submission: 01/2026

Submit clinical protocols to your IND 134859 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[6]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

[6] https://www.fda.gov/media/128163/download

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that for IMDELLTRA, you submit all U.S. cases describing adverse reactions that may be cytotoxic release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) as 15-day "Alert reports" (described under 21 CFR 600.80(c)(1)) through the 3rd year following initial U.S. approval.

We request that you provide a separate narrative summary and analysis for cases that may be ICANS or CRS, involving IMDELLTRA, in each required postmarketing periodic safety report (e.g., Periodic Adverse Experience Report [PAER] required under 21 CFR 600.80(c)(2)).

Your narrative summary and analysis should include an interval and cumulative assessment of each event and a line listing of the cases for the reporting interval. Your narrative summary should include an assessment of the following:

- The number of cases reporting a patient who experienced an event that may be CRS or ICANS involving IMDELLTRA.
- Action taken in response to an event that may be CRS or ICANS involving IMDELLTRA, including but not limited to hospitalization status, treatments administered, and supportive care.
- Outcome of an event that may be CRS or ICANS involving IMDELLTRA.
- Outcome of retreatment after event that may be CRS or ICANS involving IMDELLTRA if applicable (including prior medications given and dose received).

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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

Sincerely,

{See appended electronic signature page}

Paul Kluetz, M.D.
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

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

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

/s/

PAUL G KLUETZ
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