Our STN: BL 125789/0

ACCELERATED BLA APPROVAL
August 1, 2024

Adaptimmune LLC
Attention: Eric Dollins, PhD
351 Rouse Boulevard
Philadelphia, PA 19112

Dear Dr. Dollins:

Please refer to your Biologics License Application (BLA) received December 5, 2023, under section 351(a) of the Public Health Service Act (PHS Act) for afamitresgene autoleucel.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2315 to Adaptimmune LLC, Philadelphia, PA, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products and pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and the regulations for accelerated approval, 21 CFR 601.41. This 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 afamitresgene autoleucel, which is indicated for treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 04044768 and 03132922.

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval statutory provisions and regulations, we may grant marketing approval for a biological product on the basis of adequate and well-controlled studies establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. This approval requires you to study the

biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.

Approval under these statutory provisions and regulations requires, among other things, that you conduct adequate and well-controlled studies to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as improved overall response rate supported by duration of response.

Accelerated Approval Required Studies

We remind you of your postmarketing requirement specified in your submission of July 16, 2024.

1. Submit the Final Clinical Study Report, including datasets from ADP-0044-002 Cohorts 2 and 3, to verify and describe the clinical benefit of afamitresgene autoleucel, through more precise estimation of the overall response rate and mature response duration per independent review assessment, in adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive, and whose tumor expresses the MAGE-A4 tumor antigen as determined by FDA-approved or cleared companion diagnostic devices. Overall response rate and duration of response will be assessed by independent review and all patients will be followed for at least 15 months to assess duration of response.

   Final Protocol Submission: October 31, 2024

   Study/Trial Completion: July 31, 2025

   Final Report Submission: December 31, 2025

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of July 16, 2024.

Please submit the protocols to your IND 17235, with a cross-reference letter to this BLA, STN BL 125789 explaining that these protocols were submitted to the IND. Please refer to the sequential number for each study and the submission number as shown in this letter.

You must conduct these studies with due diligence. If required postmarketing studies fail to verify that clinical benefit is conferred by afamitresgene autoleucel, or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval.

You must submit reports of the progress of each study listed above as required under section 506(c) of the FDCA 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) of the FDCA. The initial report will be a standalone submission and the subsequent report will be combined with your application's annual status report 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. Submit the subsequent 180-day report with your application's annual status report. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.

Your 180-day report 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. 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.

Your 180-day reports, including both the standalone 180-day report submitted 180 days after the date of approval and the 180-day report submitted with your annual status report, must be clearly designated as **180-Day AA PMR Progress Report.**

FDA will consider the submission of your annual status report under section 506B(a)(1) of the FDCA and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year, to satisfy the periodic reporting requirement under section 506B(a)(2) of the FDCA. You are also required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) of the FDCA 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.

Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Postmarketing Requirements and 506B Commitments are fulfilled or released.

Please submit final study reports as a supplement to this BLA, STN BL 125789. For administrative purposes, all submissions related to these postmarketing study requirements must be clearly designated as "**Subpart E Postmarketing Study Requirements**."

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture afamitresgene autoleucel drug product at Adaptimmune LLC, 351 Rouse Boulevard, Philadelphia, PA 19112. The MAGE-A4-c1032 lentiviral vector will be manufactured by (b) (4)

You may label your product with the proprietary name TECELRA and market it in infusion bags containing (b) (4) One or more infusion bags will be supplied to meet the dose of 2.68×10^9 – 10×10^9 MAGE-A4 TCR positive T cells.

ADVISORY COMMITTEE

We did not refer your application to the Cellular, Tissue, and Gene Therapies Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefitted from an advisory committee discussion.

DATING PERIOD

The dating period for afamitresgene autoleucel shall be 6 months from the date of manufacture when stored at ≤ -130°C. The date of manufacture shall be defined as the date of final formulation of the drug product (DP). The dating period for the MAGE-A4-c1032 lentiviral vector shall be (b) (4) when stored at (b) (4)

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of afamitresgene autoleucel to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). 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.

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, 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 the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations.

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of afamitresgene autoleucel, or in the manufacturing facilities.

LABELING

Under 21 CFR 201.57(c)(18), patient labeling must be referenced in section 17 PATIENT COUNSELING INFORMATION. Patient labeling must be available and may either be reprinted immediately following the full prescribing information of the package insert or accompany the prescription product labeling.

We hereby approve the draft content of labeling including Package Insert and Medication Guide submitted on August 1, 2024 at 2:27 PM and the draft carton and container labels submitted under amendment 81 and 83, dated July 18, 2024 and July 22, 2024.

CONTENT OF LABELING

As soon as possible, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the: Package Insert and Medication Guide submitted on August 1, 2024. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels identical to the package and container labels submitted on July 18, 2024 and July 22, 2024, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using*

the eCTD Specifications at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125789 at the time of use and include implementation information on Form FDA 356h.

PROMOTIONAL MATERIALS

Please note that the accelerated approval regulation concerning promotional materials (21 CFR 601.45) stipulates that all advertising and promotional labeling items that you wish to distribute in the first 120 days following approval, must have been received by FDA prior to the approval date. After approval, promotional items intended for dissemination after the first 120 days following approval must be submitted to the FDA at least 30 days prior to the anticipated distribution date. Please submit draft materials with a cover letter noting that the items are for accelerated approval, and an accompanying FORM FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by FORM FDA 2253 (21 CFR 601.12(f)(4)).

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs* at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. In addition to the reporting requirements in 21 CFR 600.80, you must submit adverse experience reports for all secondary malignancies of T cell origin as 15-day expedited reports to the FDA Adverse Event Reporting System (FAERS). For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format — Postmarketing Safety Reports* at https://www.fda.gov/regulatory-information/search-fdaguidance-documents/providing-submissions-electronic-format-postmarketing-safetyreports and FDA's Adverse Event reporting System website at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reportingsystem-faers/fda-adverse-event-reporting-system-faers-electronic-submissions. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at https://www.fda.gov/media/89610/download.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pediatric patients under 2 years of age because the necessary studies are impossible or highly impracticable. This is because of the rarity of pediatric patients ages < 2 years with MAGE-A4 expressing solid tumors.

We are deferring submission of your pediatric study for the ages of 2 to <17 years because the product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.28 and section 505B(a)(4)(C) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an "**Annual Status Report of Postmarketing Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. This required study is listed below:

2. Conduct a molecularly targeted pediatric cancer investigation in a sufficient number of patients with solid tumors expressing MAGE-A4 to evaluate dosing, pharmacokinetics, safety, and antitumor activity of afamitresgene autoleucel following lymphodepletion with fludarabine and cyclophosphamide. The study should enroll patients aged ≥ 2 years <17 years with synovial sarcoma, malignant peripheral nerve sheath tumor, neuroblastoma, or osteosarcoma, who have received prior systemic therapy for advanced disease, and are positive for HLA-A*02:01, HLA-A*02:02, HLA-A*02:03, or HLA-A*02:06 allele.

   Final Protocol Submission Date: Completed

   Study Completion Date: April 30, 2027

   Final Report Submission Date: September 30, 2027

Submit final study reports to this BLA STN BL 125789. In order for your PREA PMR to be considered fulfilled, you must submit and receive approval of either an efficacy or a labeling supplement. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated as:

- **Required Pediatric Assessment**

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (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 (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to identify a serious risk of secondary malignancies after administration of afamitresgene autoleucel.

We have also determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess a serious risk of patient exposure to any unknown at this time leachables from the DP for afamitresgene autoleucel.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies:

3. A postmarketing, prospective, multi-center, observational study to assess and characterize the risk of secondary malignancies, and long-term safety following treatment with afamitresgene autoleucel (Study CM21-177). The study will include patients with synovial sarcoma who received afamitresgene autoleucel, and each enrolled patient will be followed for 15 years after product administration.

   We acknowledge the timetable you submitted on July 16, 2024, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: October 31, 2024

   Study Completion Date: December 31, 2044

   Final Report Submission: October 31, 2045

4. An adequate assessment of leachables in the DP including the contribution of (b) (4) major process components utilized in Step (b) (4) of the afamitresgene autoleucel manufacturing process, and an updated toxicological risk assessment once the study is completed.

   We acknowledge the timetable you submitted on July 16, 2024, which states that you will conduct this study according to the following schedule:

   Initial Protocol Submission for FDA Review: August 9, 2024

   Final Protocol Submission: September 30, 2024

   Study Completion: October 1, 2025

   Final Study Report Submission: December 31, 2025

Please submit the protocols to your IND 17235, with a cross-reference letter to this BLA, STN BL 125789 explaining that these protocols were submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to the BLA. If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement to this BLA, STN BL 125789. For administrative purposes, all submissions related to these postmarketing studies required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence Status Update under Section 505(o)**

- **Supplement contains Required Postmarketing Final Report under Section 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. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA 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 section 505(o) and 21 CFR 601.70. We remind you that to comply with section 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 periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your correspondences of July 31, 2024 as outlined below:

5. Adaptimmune LLC commits to conduct a requalification of the (b) (4) sterility test using the (b) (4) method. The final qualification study report will be submitted as a Postmarketing Commitment - Final Study Report by October 31, 2024.

   Final Study Report Submission: October 31, 2024

6. Adaptimmune LLC commits to implement storage and shipping of (b) (4) sterility samples at (b) (4) and conduct a (b) (4) study. The final study report will be submitted as a Postmarketing Commitment - Final Study Report by October 31, 2024.

   Final Study Report Submission: October 31, 2024

7. Adaptimmune LLC commits to conduct a study measuring (b) (4) process-related impurities in the afamitresgene autoleucel manufacturing process. The final study report will be submitted as a Postmarketing Commitment - Final Study Report by April 30, 2025.

   Final Study Report Submission: April 30, 2025

8. Adaptimmune LLC commits to conduct a feasibility study to investigate potential negative controls for the (b) (4) assay. The final study report will be submitted as a Postmarketing Commitment – Final Study Report by April 30, 2025.

   Final Study Report Submission: April 30, 2025

9. Adaptimmune LLC commits to providing the outstanding results of the additional shipping validation performed for the drug product (b) (4) that includes performing container closure integrity testing (CCIT) to demonstrate integrity of the drug product container after shipping. The final study report will be submitted as a Postmarketing Commitment - Final Study Report by September 30, 2024.

   Final Study Report Submission: September 30, 2024

10. Adaptimmune LLC commits to providing the results of the hypothesis testing to understand the root cause of the damage to the drug product bags observed in the initial shipping study. The final study report will be submitted as a Postmarketing Commitment - Final Study Report by September 30, 2024.

    Final Study Report Submission: September 30, 2024

11. Adaptimmune LLC commits to providing the study results of the additional container closure integrity testing using a positive control with an established

sensitivity (i.e., (b) (4) for the afamitresgene autoleucel drug product (b) (4) The final study report will be submitted as a Postmarketing Commitment - Final Study Report by September 30, 2024.

Final Study Report Submission: September 30, 2024

12. Adaptimmune LLC commits to providing a supplemental (b) (4) efficacy validation study for the (b) (4) that evaluates the (b) (4). The final study report will be submitted as a Postmarketing Commitment - Final Study Report by December 31, 2025.

    Final Study Report Submission: December 31, 2025

13. Adaptimmune LLC commits to performing an (b) (4) test using the (b) (4) assay on samples of drug substance taken at (b) (4) data reported in document number VAL 02609, Comparability of the (b) (4) assay to (b) (4) using (b) (4) controls. The final study report will be submitted as a Postmarketing Commitment - Final Study Report by December 31, 2024.

    Final Study Report Submission: December 31, 2024

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to this BLA, STN BL 125789. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Study Commitment – Correspondence Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,

- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment Final Study Report**.

POST APPROVAL FEEDBACK MEETING

New biological products 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, please contact the Regulatory Project Manager for this application.

Sincerely,

Melissa Mendoza
Director
Office of Compliance
and Biologics Quality
Center for Biologics
Evaluation and Research

Lola Fashoyin-Aje, MD, MPH
Director
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics
Evaluation and Research