Our STN: BL 125773/0

ACCELERATED BLA APPROVAL
February 16, 2024

Iovance Biotherapeutics, Inc.
Attention: Guy C. Ruble, PharmD, RAC
825 Industrial Road, Suite 400
San Carlos, CA 94070

Dear Dr. Ruble:

Please refer to your Biologics License Application (BLA) received March 27, 2023, under section 351(a) of the Public Health Service Act (PHS Act) for lifileucel.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2298 to Iovance Biotherapeutics, Inc., San Carlos, CA, 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. 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 lifileucel. Lifileucel is indicated for treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT02360579, NCT03083873, NCT03108495, NCT03645928, and NCT04614103.

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 clinical trials 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 clinical trials to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as improvement in progression free survival (PFS) and overall survival (OS).

Accelerated Approval Required Study

We remind you of your postmarketing requirement specified in your submission of February 12, 2024.

1. Complete the Phase 3, multiregional, multicenter, randomized, open-label controlled trial (IOV-MEL-301) in patients with previously untreated unresectable or metastatic melanoma. Patients will be randomized to lifileucel (LN-144) regimen in combination with pembrolizumab or to pembrolizumab monotherapy. The dual primary endpoints will be objective response rate (ORR) and progression-free survival (PFS), with overall survival (OS) as the key secondary endpoint.

   Iovance Biotherapeutics, Inc. is required to follow the following timelines:

   Final Protocol Submission: April 30, 2024

   Study Completion Date (based on final analysis of overall survival): March 31, 2030

   Final Study Report Date: March 31, 2031

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of February 12, 2024.

Please submit the protocol to your IND 16317, with a cross-reference letter to this BLA, STN BL 125773 explaining that this protocol was submitted to the IND. Please refer to the sequential number for each clinical trial and the submission number as shown in this letter.

You must conduct this clinical trial with due diligence. If required postmarketing clinical trial fails to verify that clinical benefit is conferred by lifileucel, 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 clinical trial 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) and include a summary of high-grade safety events by treatment arm. 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 report as a supplement to this BLA, STN BL 125773. For administrative purposes, all submissions related to this postmarketing study requirement must be clearly designated as "**Subpart E Postmarketing Study Requirements**."

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture lifileucel at your facilities located at Iovance Biotherapeutics Manufacturing LLC, Philadelphia, PA and (b) (4)

(b) (4) You may label your product with the proprietary name AMTAGVI and market it in 100 to 125 mL per bag in one to four containers containing 7.5 x 10^9 to 72 x 10^9 viable cells total.

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 lifileucel shall be six months from the date of manufacture when stored at less than or equal to -150°C. The date of manufacture shall be defined as the date of final formulation of the drug product. We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of lifileucel 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 lifileucel, or in the manufacturing facilities.

As previously communicated, the protocol and product quality attributes used to establish comparability between (b) (4) and Iovance Biotherapeutics Manufacturing LLC manufactured drug product will not be sufficient to establish analytical comparability after implementation of a major manufacturing change. We recommend you perform additional (b) (4) to (b) (4) and elucidate the specific mechanism of action of your drug product (b) (4). We recommend you request a formal meeting with us prior to incorporating new product quality attributes, implementing a major manufacturing change, and/or executing a comparability exercise. Your executed comparability study report(s) should be submitted as a Prior Approval Supplement. If product comparability cannot be established based on analytical comparability studies alone, additional clinical study(ies) with your drug product, AMTAGVI, may be required.

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 Patient Package Insert, submitted under amendment 87, dated February 16, 2024, and the draft carton and container labels submitted under amendment 82 and 87, dated February 9 and 16, 2024.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, 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 Patient Package Insert submitted on February 16, 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.

CARTON AND CONTAINER LABELS

Please electronically submit final printed carton and container labels identical to the carton and container labels submitted on February 9, 2024 and February 16, 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 125773 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 all adverse experience reports for uveitis, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and hemophagocytic lymphohistiocytosis (HLH), regardless of seriousness or expectedness, as 15-day expedited reports to the FDA Adverse Event Reporting System (FAERS). Uveitis, CRS, ICANS, and HLH reports must be submitted as 15-day expedited reports for 3 years following the date of product licensure. 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072369 and FDA's Adverse Event reporting System website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/PostMarketActivities/LotReleases/ucm061966.htm.

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.

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

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

We acknowledge your written commitments as described in your correspondences of January 29, 2024 and February 14, 2024, as outlined below:

2. Iovance Biotherapeutics, Inc. commits to perform a study to develop and evaluate the suitability of (b) (4) controls for (b) (4) (b) (4) analysis of (b) (4) on the drug product. This study is designed to include a comparative analysis of performance characteristics of the original control strategy (using (b) (4)) to the (b) (4) control strategy for (b) (4) in a statistically meaningful number of clinical batches manufactured at (b) (4) and Iovance Biotherapeutics Manufacturing LLC facilities. Iovance Biotherapeutics, Inc. also commits to re-evaluation of the (b) (4) commercial release acceptance criteria after completion of a statistically powered study. Iovance Biotherapeutics, Inc. will submit the study protocol, including justification for the number of batches to be used in the comparative analysis and re-evaluation of the commercial release acceptance criteria, for review and feedback as a product correspondence supplement by April 30, 2024. Iovance Biotherapeutics, Inc. will submit the final study report, which includes the validation report and justification for change to the commercial release acceptance criteria (if changes are necessary), as a Prior Approval Supplement by April 30, 2025.

   Study Protocol Submission: April 30, 2024

   Final Report Submission: April 30, 2025

3. Iovance Biotherapeutics, Inc. commits to execute a (b) (4) organic and elemental leachables study for lifileucel over the manufacturing, storage, and in-use period (i.e., for cumulative leachables in the drug product). Given the complexity of the biological product, this can be a simulated study [i.e., (b) (4) performed at (b) (4) (b) (4) and Iovance Biotherapeutics Manufacturing LLC manufacturing facilities. This study is designed to start at the manufacturing process step with high-risk for leachables (b) (4) and evaluate respective maximal hold times for the drug product during manufacturing, long-term storage including freezing up to 6 months and thawing of the bag for use, and in-use conditions. The analytical data will be assessed for safety using at least a (b) (4) safety margin, considering analytical uncertainty of the methods. Iovance Biotherapeutics, Inc. will submit the final study report as a Postmarketing Commitment – Final Study Report by February 28, 2025.

   Final Study Report Submission: February 28, 2025

4. Iovance Biotherapeutics, Inc. commits to performing the container closure integrity testing with a positive control with an established sensitivity, (i.e., a (b) (4)
   Iovance Biotherapeutics, Inc. will submit the final report as a Postmarketing Commitment – Final Report by February 28, 2025.

   Final Report Submission: February 28, 2025.

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to this BLA, STN BL 125773. 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

Nicole Verdun, MD
Acting Director
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics
Evaluation and Research