



Our STN: BL 125758/0

BLA APPROVAL

March 18, 2024

Orchard Therapeutics (Europe) Limited
Attention: Samantha Williams, PharmD, RPh
Orchard Therapeutics North America
101 Seaport Boulevard, 7th Floor
Boston, MA 02210

Dear Dr. Williams:

Please refer to your Biologics License Application (BLA) received July 19, 2023, submitted under section 351(a) of the Public Health Service Act (PHS Act) for atidarsagene autotemcel.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2263 to Orchard Therapeutics (Europe) Limited, London, United Kingdom, under the provisions of section 351(a) of the PHS 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 atidarsagene autotemcel, which is indicated for treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture atidarsagene autotemcel drug substance and drug product at (b) (4) located at (b) (4). The ARSA lentiviral vector will be manufactured at (b) (4) located at (b) (4).

You may label your product with the proprietary name LENMELDY and market it in (b) (4) bags formulated at a concentration between 2×10^6 cells/mL to 11.8×10^6 cells/mL, where each bag contains between 10-20mL in 1 to 8 bags. The minimum dose for pre-symptomatic late infantile is 4.2×10^6 CD34+ cells/kg body weight, pre-symptomatic early juvenile 9×10^6 C34+ cells/kg body weight, or early symptomatic

early juvenile 6.6×10^6 cells/kg body weight. The maximum dose is 30×10^6 CD34+ cells/kg body weight.

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 that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for atidarsagene autotemcel shall be six months from the date of manufacture when stored at $\leq -130^\circ\text{C}$ (-202°F). The date of manufacture shall be defined as the date of final formulation of the drug product (DP). The dating period for the ARSA 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 atidarsagene autotemcel 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 atidarsagene autotemcel, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including the Package Insert submitted under amendment 61, dated March 18, 2024, and the draft package and container labels submitted under amendment 60, dated March 15, 2024.

WAIVER OF 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, 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 submitted on March 15, 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 March 15, 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/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm333969.pdf>.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125758/0 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with 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 advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

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 serious adverse events as 15-day expedited reports (regardless of expectedness) to the FDA Adverse Event Reporting System (FAERS). Serious adverse event 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/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports> and FDA's Adverse Event reporting System website at <https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-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/vaccines-blood-biologics/lot-release/lot-distribution-database-idd>.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher (PRV), as provided under section 529 of the FDCA. This PRV has been

assigned a tracking number, PRV BLA 125758/0. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, **“Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”**
- This PRV may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the PRV may be transferred, but each person to whom the PRV is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this PRV, you should refer to this letter as an official record of the voucher. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our website as are all approval letters) and proof that the PRV was transferred.
- FDA may revoke the PRV if the rare pediatric disease product for which the PRV was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a PRV must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
 - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
 - the estimated demand in the U.S. for the product, and
 - the actual amount of product distributed in the U.S.

You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease PRV Program webpage available at <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.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 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 atidarsagene autotemcel.

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 extractables and leachables from the product-contact materials in the atidarsagene autotemcel manufacturing process.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks. Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies:

1. A postmarketing, prospective, observational, study to assess and characterize the risk of secondary malignancies, and long-term safety following treatment with atidarsagene autotemcel (OTL-200-12). This study will enroll a minimum of 17 subjects. The enrolled patients will be followed for 15 years after product administration.

We acknowledge the timetable you submitted on February 22, 2024, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: July 31, 2024

Study Completion Date: June 30, 2044

Final Report Submission: December 31, 2044

2. An adequate leachables safety assessment for the OTL-200 drug product (DP) through its manufacturing process, storage, and in-use conditions. This assessment must include the following:

- a. Assessment of elemental extractables from relevant DP manufacturing/storage components, and both elemental and organic leachables (i.e., cumulative) in the final DP.
- b. The leachables study can be conducted by simulating the DP manufacturing process from the step with high-risk for leachables components ((b) (4)), may include simulation of respective (b) (4) , should be conducted with all operations performed using maximal hold times and temperatures at respective steps, and continue through the product freezing, shelf-life storage, thawing, and in-use processing.
- c. This evaluation will also include a full toxicological risk assessment for the identified leachables.

Final Protocol Submission: August 31, 2024

Study Completion Date: July 31, 2025

Final Report Submission: September 30, 2025

Please submit the protocols to your IND 26917, with a cross-reference letter to this BLA, STN BL 125758/0 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 label, the final study report must be submitted as a supplement to this BLA, STN BL 125758/0. 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 under Section 505(o)**
- **Required Postmarketing Final Report 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 <http://www.fda.gov/Drugs/Guidance/ComplianceRegulatoryInformation/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 letter of March 12, 2024, as outlined below:

3. Orchard Therapeutics (Europe) Limited commits to perform a comparability study as part of the Lenmeldy drug product (b) (4)-based mycoplasma assay as required by 21 CFR 610.9. (b) (4) mycoplasma testing will be performed by (b) (4) while the (b) (4) prepared by (b) (4) will be tested by (b) (4) site in (b) (4) using the (b) (4)-based mycoplasma assay. The final validation study report will be submitted as a “Postmarketing Commitment - Final Study Report” by October 31, 2024.

Final Report Submission: October 31, 2024

- Orchard Therapeutics (Europe) Limited commits to provide additional sterility validation data evaluating the test sample handling manipulation. The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by October 31, 2024.

Final Report Submission: October 31, 2024

- Orchard Therapeutics (Europe) Limited commits to perform an additional validation study to assess the performance of the (b) (4) assay in the clinically relevant range. The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by July 31, 2024.

Final Report Submission: July 31, 2024

- Orchard Therapeutics (Europe) Limited commits to perform additional robustness assessments of the (b) (4) assays. The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by May 31, 2024.

Final Report Submission: May 31, 2024

- Orchard Therapeutics (Europe) Limited commits to perform additional robustness assessments of the (b) (4) assay. The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by October 31, 2024.

Final Report Submission: October 31, 2024

- Orchard Therapeutics (Europe) Limited commits to perform additional robustness assessments of the (b) (4). The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by October 31, 2024.

Final Report Submission: October 31, 2024

- Orchard Therapeutics (Europe) Limited commits to perform additional robustness assessments of the (b) (4) assay used to (b) (4). The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by October 31, 2024.

Final Report Submission: October 31, 2024

- Orchard Therapeutics (Europe) Limited commits to revalidate the (b) (4) assay to include the range of the commercial lot release criterion. The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by October 31, 2024.

Final Report Submission: October 31, 2024

11. Orchard Therapeutics (Europe) Limited commits to validate the appearance testing assay and reassess the lot release criterion. The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by July 31, 2024.

Final Report Submission: July 31, 2024

12. Orchard Therapeutics (Europe) Limited commits to perform validation of the (b) (4) used for the (b) (4) that are utilized in the aseptic manufacturing process of the OTL-200 DP drug product, in addition to performing (b) (4) testing. The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by September 30, 2024.

Final Report Submission: September 30, 2024

13. Orchard Therapeutics (Europe) Limited commits to submit a container closure integrity test (CCIT) study to demonstrate the integrity of the (b) (4) with the inclusion of a positive control with (b) (4). The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by December 31, 2024.

Final Report Submission: December 31, 2024

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125758/0. 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 – 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 Commitment – 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, JD
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