Our STN: BL 125874/0

ACCELERATED BLA APPROVAL
April 23, 2026

Regeneron Pharmaceuticals, Inc.
Attention: Boning Zhao, PharmD
777 Old Saw Mill River Rd
Tarrytown, NY 10591

Dear Dr. Zhao:

Please refer to your Biologics License Application (BLA) received December 23, 2025, under section 351(a) of the Public Health Service Act (PHS Act) for lunsotogene parvec-cwha.

LICENSING

Effective this date, we have approved your BLA for lunsotogene parvec-cwha (biologic) and the associated drug product Administration Kit (device), under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and the regulations for accelerated approval, 21 CFR 601.41. You are hereby authorized to introduce or deliver for introduction into interstate commerce, lunsotogene parvec-cwha and Administration Kit under your existing Department of Health and Human Services U.S. License No. 1760. Lunsotogene parvec-cwha is indicated for the treatment of pediatric and adult patients with severe-to-profound and profound sensorineural hearing loss (any frequency >90 dB HL) associated with molecularly confirmed biallelic variants in the *OTOF* gene, preserved outer hair cell function, and no prior cochlear implant in the same ear.

The review of this product was associated with the following National Clinical Trial (NCT) number: NCT05788536.

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval statutory provisions and regulations we may grant marketing approval for a biological product on the basis of an adequate and well-controlled study 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 an adequate and well-controlled study to verify and describe clinical benefit attributable to this product. Clinical benefit in *OTOF*-associated hearing loss is evidenced by effects such as durable hearing restoration based on long-term improvements on pure-tone audiometry (PTA) testing and positive effects on speech/language development and activities of daily living/quality of life assessments.

Accelerated Approval Required Studies

We remind you of your postmarketing requirement specified in your submission of April 2, 2026.

1. Submit analyses of clinical outcomes in: 1) at least 30 lunsotogene parvec-cwha-treated pediatric patients (unilateral or bilateral treatment) enrolled in Study DB-OTO-001 with *OTOF* gene-associated sensorineural hearing loss after 104 weeks post product administration; including 2) at least 5 lunsotogene parvec-cwha newly treated patients 16 years of age or older, with *OTOF* associated sensorineural hearing loss (enrolled either within the same trial or in a separate trial). The analyses should evaluate at a minimum the following clinical outcomes: hearing sensitivity threshold by PTA, age-appropriate speech and language outcome measures, auditory brainstem response (ABR), global impression of improvement (GII) clinical scales, and quality of life (QoL) scales. These analyses should compare data from treated patients to comparable, untreated patients with the same diagnosis followed over a similar duration of follow up for purposes of verifying and describing the clinical benefit of lunsotogene parvec-cwha in pediatric and adult patients with *OTOF* gene-associated sensorineural hearing loss.

   Final Protocol Submission Date: December 30, 2026
   Study Completion Date: April 30, 2030
   Final Report Submission Date: August 30, 2030

We expect you to complete the design, initiation, and accrual for this study with due diligence and to complete and submit reports of the study results within the framework described herein.

Please submit the protocol to your IND 28864, with a cross-reference letter to this BLA, STN BL 125874 explaining that this protocol was 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 this study with due diligence. If the required postmarketing study fails to verify that clinical benefit is conferred by lunsotogene parvec-cwha, 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 (with a 60-day grace period). 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 (subject to a 60-day grace period), 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(s) as a supplement to this BLA, STN BL 125874. 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 lunsotogene parvec-cwha drug substance at (b) (4) .
The final formulated product will be manufactured and filled at (b) (4) and labeled and packaged at the (b) (4) You are approved to assemble the Administration Kit at (b) (4)

You may label your product with the proprietary name OTARMENI and market it in single-dose vials containing 0.63 mL extractable volume at a concentration of 3 x 10^{13} vector genomes/mL. Your Administration Kit must be labeled with "USE ONLY WITH OTARMENI" and contain the following: one Becton Dickinson (BD) (b) (4) -gauge needle (K021475), one BD 1mL Luer-Lok™ syringe (K162081), one BD 3mL Luer-Lok™ syringe (K182589), one BD syringe cap (510(k) exempt), and one Vygon Premicath® (b) (4) catheter (K954302/K041468).

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 lunsotogene parvec-cwha shall be 18 months from the date of manufacture when stored at -80°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be (b) (4) when stored at (b) (4) The expiration date for the Administration Kit is determined by the earliest expiring component among all items packaged in the carton but cannot exceed 9 months from the date of catheter manufacturing.

FDA LOT RELEASE

Please submit protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

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 lunsotogene parvec-cwha, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including the Package Insert submitted under amendment 102, dated April 6, 2026, and the draft carton and container labels submitted under amendment 102, dated April 6, 2026.

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 April 6, 2026. 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 April 6, 2026, 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 125874 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 cases of malignancies as 15-day expedited reports to the FDA Adverse Event Reporting System (FAERS). Reports for malignancies must be submitted as 15-day expedited reports for three 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 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.

For information on the postmarketing safety reporting requirements for combination products as described in 21 CFR 4, Subpart B, and the dates by which combination product applicants must comply with these requirements, please refer to the Postmarketing Safety Reporting for Combination Products webpage available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

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 125874/0. 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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your correspondence of April 2, 2026, as outlined below:

2. Conduct a prospective, longitudinal, observational study to characterize the long-term safety of lunsotogene parvec-cwha in a minimum of 50 patients, including patients from the ongoing Study DB-OTO-001. Propose and justify the number

of adult patients to be enrolled in the study. All patients will be followed for a minimum of 10 years from product administration. The study will assess the incidence of serious adverse events including the risk of malignancy at pre-specified time intervals and assessments. In addition to annual PMC reports, interim study reports will be submitted to the BLA at 3 years and 6 years and should include, at least: cumulative counts of patients enrolled and their demographics, SAEs, deaths, all AEs, and malignancies; and for each SAE and malignancy, patient age and other demographics, descriptions of the event, time to onset after DB-OTO administration, diagnostic testing, diagnosis, treatment, and laboratory analysis (including insertional site testing).

Final Protocol Submission Date: August 31, 2026
Interim Study Report #1 Date: December 31, 2029
Interim Study Report #2 Date: December 31, 2032
Study Completion Date: December 31, 2039
Final Report Submission Date: June 30, 2040

Please submit clinical protocols to your IND 28864, and a cross-reference letter to this BLA, STN BL 125874 explaining that this protocol was submitted to the IND.

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement. 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 study subject to the reporting requirements of 21 CFR 601.70, 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 commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, 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.

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

We acknowledge your written commitments as described in your correspondence of April 2, 2026, as outlined below:

3. Regeneron commits to assessing (b) (4) from DB-OTO Drug Product (DP), stored at ≤ -80°C for (b) (4) months, using adequately qualified assays. A final study report will be submitted in a "Postmarketing Study Commitment – DP (b) (4) Final Study Report" by December 31, 2027.

   Final Study Report Submission Date: December 31, 2027

4. Regeneron commits to assessing the robustness of the (b) (4) lot release test for the (b) (4) A final study report will be submitted as a "Postmarketing Study Commitment – (b) (4) Robustness Assessment Final Study Report" by September 30, 2026.

   Final Study Report Submission Date: September 30, 2026

5. Regeneron commits to conducting a study to re-evaluate the maximum (b) (4) for DB-OTO Drug Product (DP) and Labeled Drug Product (LDP) manufacturing processes according to the study protocol outlined in VV-IOPS-190989 V:2.0 (Evaluation of the Maximum (b) (4) for DB-OTO DP and LDP Manufacturing Processes). Regeneron will submit the study results as a "Postmarketing Study Commitment – (b) (4) Final Study Report" by November 30, 2026.

   Final Study Report Submission Date: November 30, 2026

6. Regeneron commits to implementing a drug product-specific assay control for the relative potency assay. The final study report will establish acceptance criteria for the assay control as part of potency assay suitability criteria and include updated standard operating procedure (SOP) that implements the assay control along with finalized system suitability criteria.

   The study results, analysis of the data to support the assay control suitability criteria, and the updated relative potency assay SOP will be submitted as a "Postmarketing Study Commitment – Assay Control for Relative Potency Final Study Report" by May 31, 2026.

Final Study Report Submission Date: May 31, 2026

7. Regeneron commits to reassessing the acceptance criteria for release testing of lunsotogene parvec-cwha drug substance and drug product based on manufacturing experience and revising the acceptance criteria, if appropriate. A final acceptance criteria reassessment report will be submitted as a "Postmarketing Study Commitment – Re-assessment of Lot Release Acceptance Criteria Final Study Report" after CBER lot release of (b) (4) drug product batches including PPQ lot(s) that are released for commercial distribution. If (b) (4) commercial lots have not been manufactured by December 31, 2027, Regeneron will provide an updated timeline for reassessing the lot release acceptance criteria using (b) (4) commercial lot data.

   Final Study Report Submission Date: December 31, 2027

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to this BLA, STN BL 125874. 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 Managers for this application.

Sincerely,

Asha Das, MD
Director
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and Research