Our STN: BL 125827/0

ACCELERATED BLA APPROVAL
AUGUST 6, 2026

Replimune, Inc.
Attention: Kari Jeschke
500 Unicorn Park Drive, Third Floor
Woburn, MA 01801

Dear Kari Jeschke:

Please refer to your Biologics License Application (BLA) received November 21, 2024, under section 351(a) of the Public Health Service Act (PHS Act) for vusolimogene oderparepvec-wtpg.

We acknowledge receipt of your amendment dated June 2, 2026, which constituted a complete response to our April 10, 2026 action letter.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2360 to Replimune, Inc., Woburn, MA, 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 vusolimogene oderparepvec-wtpg. vusolimogene oderparepvec-wtpg is indicated in combination with nivolumab for treatment of adult patients with unresectable advanced cutaneous melanoma who experienced disease progression with a programmed death receptor-1 (PD-1)-blocking antibody-based regimen.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT03767348, NCT04050436, NCT04349436.

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 clinical trial 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 clinical trial to verify and describe the clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as increased survival.

Accelerated Approval Required Study

We remind you of your postmarketing requirement specified in your submission of August 5, 2026.

1. Replimune, Inc. is required to complete the IGNYTE-3 (RP1-104) trial (NCT06264180), an ongoing Phase 3 multicenter, multiregional, randomized, controlled, open-label confirmatory trial to evaluate the safety and efficacy of vusolimogene oderparepvec in combination with nivolumab compared with treatment of physician's choice in patients with unresectable advanced cutaneous melanoma who have confirmed disease progression on an anti-PD-1 and an anti-CTLA-4 either in combination or in sequence. Overall survival is the primary endpoint. Approximately 400 patients will be randomized at 1:1 ratio to the two treatment arms.

   Final Protocol Submission: August 31, 2026

   Study/Trial Completion: September 2030

   Final Report Submission: March 2031

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of August 5, 2026.

Please submit the protocol to your IND 17922, with a cross-reference letter to this BLA, STN BL 125827 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 the required postmarketing clinical trial fails to verify that clinical benefit is conferred by vusolimogene oderparepvec-wtpg, or is 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 (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 125827. 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 vusolimogene oderparepvec-wtpg at your facility located at 33 New York Ave., Suite 100, Framingham, MA 01701, United States. You may label your product with the proprietary name TUDRIQEV and market it

in single-dose vials containing 1.0 mL extractable volume at concentrations of 10^6 Plaque Formation Unit (PFU)/mL and 10^7 PFU/mL.

DATING PERIOD

The dating period for vusolimogene oderparepvec-wtpg shall be 48 months from the date of manufacture when stored at -80°C ± 10°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)

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, and 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 vusolimogene oderparepvec-wtpg, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert submitted under amendment 128, dated August 6, 2026, Patient Package Insert submitted under amendment 127, dated August 5, 2026, and the draft carton and container labels submitted under amendment 98, dated June 26, 2025.

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 August 6, 2026, and Patient Package Insert submitted on August 5, 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 June 26, 2025 (amendment 98), 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 125827 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. 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.

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 12 years of age with melanoma because necessary studies are impossible or highly impracticable. This is because melanoma is rare in pediatric patients in this age group.

We are deferring submission of your pediatric study for pediatric patients 12 years of age and older for this application because this 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 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 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. Replimune, Inc is required to conduct an assessment of vusolimogene oderparepvec in combination with nivolumab in pediatric patients 12 years of age and older with advanced melanoma who have confirmed disease progression on an anti-PD-1 and anti-CTLA-4 in combination or in sequence to support the identification of the safe and effective dose in this population. The required pediatric assessment will be conducted through the Phase 3 confirmatory IGNYTE-3 (RP1-104) trial (NCT06264180). Refer to PMR #1 above for the required timelines.

   Final Protocol Submission: August 31, 2026

   Study Completion Date: September 2030

   Final Report Submission: March 2031

Submit the protocol to your IND 17922, with a cross-reference letter to this BLA, STN BL 125827 explaining that this protocol was submitted to the IND.

Submit final study reports to this BLA STN BL 125827. 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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitment(s) as described in your correspondence on August 5, 2026, as outlined below:

3. Replimune commits to re-evaluate the (b) (4) acceptance criterion for release testing of TUDRIQEV (b) (4) based on manufacturing experience when data from (b) (4) total PPQ and post-PPQ batches are available and revise the acceptance criterion if appropriate. The final re-evaluation report will be submitted as a "Postmarketing Study Commitment - (b) (4) Acceptance Criterion Final Study Report." within 60 days after release of the (b) (4) (b) (4) batch.

   Final study report submission date: July 31, 2028.

4. Replimune commits to re-assess the (b) (4) based on data from (b) (4) (b) (4) according to study protocol 1131-0157 Rev.01.

   Replimune will submit the final study report as a "Postmarketing Study Commitment – (b) (4) Final Study Report".

   Final study report submission date: December 31, 2026

5. Replimune commits to conduct in-use stability study to support a maximum hold duration in syringe for 2 hours after storage of thawed TUDRIQEV drug product under the worst case conditions according to Section 16.2 Table 6 of the approved USPI. Replimune will submit the final study report as a "Postmarketing Study Commitment – In-use Stability Final Study Report" and revise the hold duration in the syringe in the USPI as supported by the in-use stability data.

   Final study report submission date: December 31, 2026.

6. Replimune commits to provide the leachables analytical data and associated toxicological assessment (for (b) (4) compounds) from ongoing leachable assessment study with drug product stability lot(s) at 24-, 36-, 48- and (b) (4) month timepoints.

   Final report of 36-month data submission date: October 31, 2026

   Final report of 48-month data submission date: October 31, 2027

Final report of (b) (4)-month data submission date: October 31, 2028

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to this BLA, STN BL 125827. 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,

Vincent Amatrudo, JD
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics
Evaluation and Research

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

Label Enclosure