Our STN: BL 125787/457

SUPPLEMENT APPROVAL
RELEASE FROM POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT
July 1, 2026

Vertex Pharmaceuticals, Inc.
Attention: Brett Richardson
50 Northern Avenue
Boston, MA 02210

Dear Brett Richardson:

We have approved your request received April 24, 2026, to supplement your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for exagamglogene autotemcel to expand the current indication to include treatment of sickle cell disease (SCD) with recurrent vaso-occlusive crises and transfusion-dependent thalassemia (TDT) in patients ages 2 to <12 years.

The review of this supplement was associated with the following National Clinical Trial (NCT) numbers: NCT05356195 and NCT05329649.

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 the Package Insert submitted under amendment 15, dated June 30, 2026, and the Patient Package Insert submitted under amendment 10, dated June 5, 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 June 30, 2026, and the Patient Package Insert submitted on June 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.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125787 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)).

For each pending supplemental application for this BLA that includes proposed revised labeling, please submit an amendment to update the proposed revised labeling with the changes approved today.

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.

RELEASE FROM POSTMARKETING REQUIREMENT

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 assess an unexpected serious risk of secondary malignancies and off-target effects following genome editing after administration of exagamglogene autotemcel. Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk.

We also refer to your submission received June 12, 2026, agreeing to a new PMR to expand the age range, and to be released from the following postmarketing requirement (PMR) identified in the December 08, 2023, approval letter.

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PMR #1 A postmarketing, prospective, multicenter observational study to assess and characterize the risks of secondary malignancies and off-target effects following genome editing occurring after treatment with exagamglogene autotemcel, and to assess the long-term safety of exagamglogene autotemcel. The study will include 250 subjects with SCD who received/will receive exagamglogene autotemcel, and each enrolled subject will be followed for 15 years after product administration. The study design will include monitoring (at prespecified intervals) with adequate testing strategies (Study Protocol VX22-290-101).

Final Protocol Submission: March 31, 2024

Study Completion: December 31, 2042

Final Study Report Submission: December 31, 2043

We have completed the review of your submission and conclude that you are released from the above PMR because the study duration will not be sufficient to monitor subjects in the expanded age range (ages 2 years and above) for long-term safety outcomes. A new PMR will be issued to include a longer study duration.

The above PMR is now considered closed and will be replaced by the new PMR described below.

NEW POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

1. A postmarketing, prospective, multicenter observational study to assess and characterize the risks of secondary malignancies and off-target effects following genome editing occurring after treatment with exagamglogene autotemcel, and to assess the long-term safety of exagamglogene autotemcel. The study will include 250 subjects with SCD and 150 subjects with TDT who received/will receive exagamglogene autotemcel, and each enrolled subject will be followed for 15 years after product administration. The study design will include monitoring (at prespecified intervals) with adequate testing strategies (Study Protocol VX22-290-101).

   We acknowledge the timetable you submitted on June 12, 2026, which states that you will conduct this study, according to the following schedule:

   Final Protocol Submission: Completed (Submitted June 12, 2026)

   Study Completion: December 31, 2045

   Final Study Report Submission: December 31, 2046

Please submit the protocol to your IND 18143, with a cross-reference letter to this BLA 125787/457 explaining that this protocol was submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement to this BLA 125787/457. For administrative purposes, all submissions related to this postmarketing study 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 the approval of this BLA 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/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

We will include information contained in the above-referenced supplement in your BLA file.

Sincerely,

Bindu George, MD
Acting Director
Division of Clinical Evaluation Hematology
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and Research