Our STN: BL 125787/0

BLA APPROVAL
December 08, 2023

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

Dear Mr. Richardson:

Please refer to your Biologics License Application (BLA) received April 03, 2023, submitted under section 351(a) of the Public Health Service Act (PHS Act) for exagamglogene autotemcel (exa-cel).

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2279 to Vertex Pharmaceuticals Inc, Boston, MA, 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 exagamglogene autotemcel which is indicated for treatment of sickle cell disease (SCD) in patients 12 years of age or older with recurrent vaso-occlusive crises (VOCs).

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 04208529 and 03745287.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture exagamglogene autotemcel drug substance and drug product at (b) (4)
(b) (4)

You may label your product with the proprietary name CASGEVY and market it in 20 mL vials containing 4 to 13 × 10^6 CD34+ cells/mL frozen in 1.5 to 20 mL of solution. The minimum dose is 3 × 10^6 CD34+ cells per kg of body weight, which may be contained within multiple vials.

DATING PERIOD

The dating period for exagamglogene autotemcel shall be 18 months from the date of manufacture when stored in the vapor phase of liquid nitrogen at ≤ -135°C (≤ -211°F). The date of manufacture shall be defined as the date of final formulation of the drug product. The dating period for the SPY101 gRNA shall be (b) (4) when stored at (b) (4) The dating period for Cas9 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 exagamglogene 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 exagamglogene autotemcel, or in the manufacturing facilities.

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 103, December 07, 2023, and carton and container labels, submitted under amendment 99, December 01, 2023.

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 December 07, 2023. 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 December 01, 2023 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/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125787/0 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 secondary malignancies and off-target effects following genome editing as 15-day expedited reports to the FDA Adverse Event Reporting System (FAERS). 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-ldd.

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 125787. 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 biologics license 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 biologics license 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 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.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies:

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).

We acknowledge the timetable you submitted on November 02, 2023, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: March 31, 2024

Study Completion: December 31, 2042

Final Study Report Submission: December 31, 2043

2. Conduct studies to comprehensively assess and screen for the impact of sequence heterogeneity on the risk of off-target editing in the patient population for exagamglogene autotemcel. Specifically,

    i. Perform a new in silico off-target analysis using publicly available databases/datasets to allow for inclusion of more variants. Specifically, perform the analysis using all variants with at least 0.5%

allele frequency in at least one of the five continental groups (Africa, Europe, East Asia, South Asia, and the Americas).

ii. Perform confirmatory testing, as appropriate and feasible, of all the off-target loci nominated from the new in silico analysis from (i) as well as those that were not accounted for in the previous study using appropriate samples harboring variants.

a. Screen for the presence of all previously identified variants (e.g., CPS1) as well as any variants identified in study (i) and (ii) in the patients treated in Studies 121, 111, 141, 151, 161, and 171.

b. For patients with a confirmed variant(s), assess for indels and chromosomal changes at each respective locus in appropriate samples.

We acknowledge the timetable you submitted on December 01, 2023 which states that you will conduct this study according to the following schedule:

Final Protocol Submission (submitted): December 01, 2023

Study Completion Date: June 30, 2032

Final Report Submission: June 30, 2032

Please submit the protocols to your IND 18143, with a cross-reference letter to this BLA, STN BL 125787/0 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 125787/0. 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/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.

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

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

We acknowledge your written commitments as described in your letters of November 20, 2023, as outlined below:

3. Vertex Pharmaceuticals, Inc., commits to perform a supplemental shipping validation study of exa-cel assessing the quality attributes including (b) (4) (b) (4) for (b) (4)

(b) (4)-transportation samples using the (b) (4) (b) (4) commercial shippers. The final validation study report will be submitted as a Postmarketing Commitment-Final Study Report by May 31, 2024.

Final Report Submission: May 31, 2024

4. Vertex Pharmaceuticals, Inc., commits to perform a supplemental (b) (4) hold time stability study in which additional data are obtained to support the hold time proven acceptable ranges, including the cumulative proven acceptable hold time. The final validation study 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 nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125787/0. 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 J. Mendoza, JD
Director
Office of Compliance and Biologics Quality
Center for Biologics
Evaluation and Research

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