Our STN: BL 125788/0

BLA APPROVAL
December 08, 2023

bluebird bio, Inc.
Attention: Megan Parsi, MBS
455 Grand Union Boulevard
Somerville, MA 02145

Dear Ms. Parsi:

Please refer to your Biologics License Application (BLA) received April 21, 2023, submitted under section 351(a) of the Public Health Service Act (PHS Act) for lovotibeglogene autotemcel.

LICENSING

We have approved your BLA for lovotibeglogene autotemcel effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, lovotibeglogene autotemcel under your existing Department of Health and Human Services U.S. License No. 2160. Lovotibeglogene autotemcel is indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events (VOEs).

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 02140554, 02151526, 04293185, and 04628585.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture lovotibeglogene autotemcel drug substance and drug product at (b) (4) The BB305 lentiviral vector will be manufactured at (b) (4)

You may label your product with the proprietary name LYFGENIA and market it in infusion bags containing 1.7 – 20×10^6 cells/mL (b) (4) - 20×10^6 CD34+ cells/mL) in approximately 20 mL of solution. The minimum dose is 3.0×10^6 CD34+ cells/kg patient 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 lovotibeglogene autotemcel shall be 12 months from the date of manufacture when stored at ≤ -140°C. The date of manufacture shall be defined as the date of final formulation of the drug product. The dating period for the BB305 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 lovotibeglogene 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 lovotibeglogene 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 Medication Guide submitted under amendment 43, dated December 07, 2023 and the draft carton and container labels submitted under amendment 35, dated 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 Medication Guide 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.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels identical to the package 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 125788/0 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 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

Your request for a rare pediatric disease priority review voucher has been denied. Although your biological product has a rare pediatric disease designation, you did not qualify for the voucher because your application did not meet the requirements to be a "rare pediatric disease product application" under section 529(a)(4) of the Federal Food, Drug & Cosmetic Act (FD&C Act) for the following reason:

FDA has determined that BLA 125788 is not a human drug application for a biological product that contains no active ingredient that has been previously approved in any other application under section 351(a) or 351(k) of the PHS Act. Specifically, BLA 125788 is for a biological product that contains an active ingredient that was previously

approved in another application under section 351(a) of the PHS Act. The active ingredient was previously approved, on August 17, 2022, in BLA 125717 for Zynteglo (betibeglogene autotemcel).

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 assess a known serious risk of secondary malignancies after administration of lovotibeglogene 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 (b) (4) bag used to store and administer lovotibeglogene autotemcel.

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, multi-center, observational study, to assess and characterize the risk of secondary malignancies after treatment with lovotibeglogene autotemcel and to assess the long-term safety of lovotibeglogene autotemcel (Study REG-503). The study will include 250 patients with sickle cell disease who received lovotibeglogene autotemcel, and each enrolled patient will be followed for 15 years after product administration. The study design will include monitoring (at pre-specified intervals) for clonal expansion with adequate testing strategies.

We acknowledge the timetable you submitted on November 29, 2023, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: March 29, 2024

Study Completion Date: December 31, 2043

Final Report Submission: December 31, 2044

2. A study to evaluate leachables of the (b) (4) bag over the duration of the shelf-life of lovotibeglogene autotemcel. This evaluation will also include a full toxicological risk assessment for the identified leachables and extractables.

We acknowledge the timetable you submitted on November 08, 2023, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 26, 2024

Study Completion Date: January 30, 2025

Final Report Submission: March 30, 2025

Please submit the protocols to your IND 15905, with a cross-reference letter to this BLA, STN BL 125788/0, 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 125788/0. 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.

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

We acknowledge your written commitment as described in your letter of November 21, 2023 as outlined below:

3. Bluebird bio, Inc., 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 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 125788/0. 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,

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