Our STN: BL 125755/0

ACCELERATED BLA APPROVAL
September 16, 2022

bluebird bio, Inc.
Attention: Denise Schultz, MS
Director, Regulatory CMC
455 Grand Union Boulevard
Somerville, MA 02145

Dear Ms. Schultz:

Please refer to your Biologics License Application (BLA) received October 18, 2021, under section 351(a) of the Public Health Service Act (PHS Act) for elivaldogene autotemcel.

LICENSING

Effective this date, we have approved your BLA for elivaldogene autotemcel, according to the regulations for accelerated approval, 21 CFR 601.41. You are hereby authorized to introduce or deliver for introduction into interstate commerce, elivaldogene autotemcel under your existing Department of Health and Human Services U.S. License No. 2160. Elivaldogene autotemcel is indicated to slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD).

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 01896102; 02698579; and 03852498.

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval regulations we may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials 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 elivaldogene autotemcel 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 regulations requires, among other things, that you conduct adequate and well-controlled clinical trials to verify and describe clinical benefit

attributable to this product. Clinical benefit is evidenced by effects such as event-free survival (i.e., alive without Major Functional Disability (MFD) or need for hematopoietic stem cell transplant (HSCT)) and stable neurologic function.

Accelerated Approval Required Studies

We remind you of your postmarketing requirements specified in your submission of September 16, 2022.

1. Follow all subjects who received elivaldogene autotemcel in Studies ALD-102 and ALD-104 to assess event-free survival (i.e., alive without Major Functional Disability (MFD) or need for hematopoietic stem cell transplant (HSCT)) for a minimum of ten years following administration of elivaldogene autotemcel.

   Final Protocol Submission: January 31, 2023

   Interim Clinical Study Report Submission: July 31, 2027

   Final Study Report Submission: July 31, 2032

2. Investigate event-free survival for at least five years post-treatment in 24 boys with more advanced early active, cerebral adrenoleukodystrophy (CALD) [(based on baseline Loes scores and Neurologic Function Score (NFS)] who will be newly treated with elivaldogene autotemcel (SKYSONA).

   Final Protocol Submission: January 31, 2023

   Study fully enrolled by: June 30, 2033

   Study Completion date: June 30, 2038

   Final Study Report Submission: December 31, 2038

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of September 16, 2022.

You must conduct these studies with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by elivaldogene autotemcel, or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43 (b), withdraw or modify approval if:

- A postmarketing clinical study fails to verify clinical benefit
- The applicant fails to perform the required postmarketing study with due diligence
- Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product

- The applicant fails to adhere to the postmarketing restrictions agreed upon
- The promotional materials are false or misleading
- Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

Please submit the protocols to your IND 15433, with a cross-reference letter to this BLA, STN BL 125755/0 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.

Your accelerated approval postmarketing required studies are subject to the reporting requirements of 21 CFR 601.70, and 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.

Please submit final study reports as a supplement to this BLA, STN BL 125755/0. For administrative purposes, all submissions related to these postmarketing study requirements must be clearly designated as "Subpart E Postmarketing Study Requirements."

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture elivaldogene autotemcel drug substance and drug product at Lonza Houston, Inc., 14905 Kirby Drive, Houston, TX 77047, U.S., and Lenti-D lentiviral vector at (b) (4)

You may label your product with the proprietary name SKYSONA and market it in infusion bags containing 4 to 30 × 10^6 cells/mL (3.6 to 30 × 10^6 CD34+ cells/mL) frozen in approximately 20 mL of solution. The minimum dose is 5.0 x 10^6 CD34+ cells/kg patient weight.

DATING PERIOD

The dating period for elivaldogene autotemcel shall be 9 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 Lenti-D 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 elivaldogene 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 elivaldogene autotemcel, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert and Medication Guide submitted September 16, 2022, and the draft carton and container labels submitted on August 17, 2022 (patient identifier bag label, BLA 125755/0, SN 0093) and September 1, 2022 (cassette and bag label, BLA 125755/0, SN 00109).

WAIVER OF HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 September 16, 2022. 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 August 17, 2022 (patient identifier bag label, BLA 125755/0, SN 0093) and September 1, 2022 (cassette and bag label, BLA 125755/0, SN 00109), 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 125755/0 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072369 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/Post-MarketActivities/LotReleases/ucm061966.htm.

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 125755/0. All correspondence 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 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 elivaldogene autotemcel.

We have also determined that such an analysis 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 elivaldogene 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:

3. A postmarketing, prospective, multi-center, observational study to assess the long-term safety of elivaldogene autotemcel and the risk of secondary malignancies occurring after treatment with elivaldogene autotemcel. The study will include at least 120 cerebral adrenoleukodystrophy patients and the enrolled patients 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 September 9, 2022, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: December 31, 2022

Study Completion Date: April 30, 2047

Final Report Submission: April 30, 2048

4. A study to support the extractable data provided for the (b) (4) bag, including the sample processing steps in the (b) (4) and an appropriate identification process used for the extractables.

We acknowledge the timetable you submitted on August 17, 2022, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: November 30, 2022

Study Completion Date: February 28, 2023

Final Report Submission: April 30, 2023

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

We acknowledge the timetable you submitted on August 17, 2022, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: November 30, 2022

Study Completion: January 30, 2024

Final Study Report Submission: March 30, 2024

Please submit the protocols to your IND 15433, with a cross-reference letter to this BLA, STN BL 125755/0 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 labeling, the final study report must be submitted as a supplement to this BLA, STN BL 125755. 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 Status Update 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 https://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 commitments as described in your letters of June 30, 2022, August 17, 2022, August 26, 2022, and August 31, 2022 as outlined below:

6. bluebird bio, Inc., commits to qualify a (b) (4) test of their (b) (4) (b) (4) to provide greater (b) (4) assurance of their final drug product and to submit these qualification results as a supplement to their file on or before March 31 of 2023.

   Final Report Submission: March 31, 2023

7. bluebird bio commits to provide a final report of the (b) (4) method qualification results using (b) (4) from the drug product manufacturing facility.

Final Report Submission: October 31, 2022

8. bluebird bio, Inc., commits to establish the sensitivity of (b) (4) method for the (b) (4) bag.

   Final Report Submission: February 28, 2023

9. bluebird bio, Inc., commits to perform the additional robustness assessments of the (b) (4) assays as described in BLA 125755.

   Final Report Submission: June 30, 2023

10. bluebird bio, Inc., commits to add testing of eli-cel cryopreserved drug product (DP) for (b) (4) as described in BLA 125755.

    Final Report Submission: February 28, 2023

11. bluebird bio, Inc., commits to perform a supplemental in-use stability study of eli-cel assessing the stability of (b) (4) under the intended conditions as described in BLA 125755.

    Final Report Submission: March 31, 2023

12. bluebird bio, Inc., commits to assess the feasibility of detecting (b) (4) The feasibility assessment will include a proposed path forward for completing a leachable study for the (b) (4), including a date the final leachable study report will be submitted to the FDA.

    Final Feasibility Assessment Report Submission: February 28, 2023

13. bluebird bio, Inc., commits to conducting (b) (4) testing following the conditions outlined in (b) (4) and provide justifications for the test method, results, and conclusions as part of a complete test report. Complete test reports for this (b) (4) testing on the (b) (4) bag will be submitted as a final study report by December 31, 2022.

    Final Report Submission: December 31, 2022

14. bluebird bio, Inc., commits to perform a (b) (4) study to evaluate drug product bag integrity following (b) (4) (e.g., (b) (4)

(b) (4) . The testing will include (b) (4) Complete test reports for this testing will be submitted as a final study report by December 31, 2022.

Final Report Submission: December 31, 2022

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to this BLA, STN BL 125755/0. 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 – 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,

Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research