Our STN: BL 125714/205

SUPPLEMENT APPROVAL
03-21-2024

Juno Therapeutics, Inc., a Bristol-Myers Squibb Company
Attention: Megan Fitzgerald
1000 Dexter Ave. N., Suite 1200
Seattle, WA 98109

Dear Megan Fitzgerald:

Please refer to your supplement to your Biologics License Application (BLA) received September 13, 2023, submitted under section 351(a) of the Public Health Service Act (PHS Act) for lisocabtagene maraleucel .

We also refer to our supplement approval letter dated March 14, 2024, which contained the following errors:

Post marketing requirement numbering and for the Accelerated PMR, we have added the last day of each month for the milestone.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain March 14, 2024, the date of the original supplement approval letter.

We have approved your request received September 13, 2023, to supplement your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for lisocabtagene maraleucel, to support a new indication in relapsed/ refractory chronic lymphocytic leukemia or small lymphocytic lymphoma in patients who have received at least two prior lines of therapy including a Bruton's tyrosine kinase (BTK) inhibitor and a B-cell lymphoma-2 (BCL-2) inhibitor, according to the regulations for accelerated approval, 21 CFR 601.41.

We have also approved a major modification to the approved Risk Evaluation and Mitigation Strategy (REMS) to minimize the burden on the healthcare delivery system of complying with the REMS.

The review of this supplement was associated with the following National Clinical Trial (NCT) numbers: NCT03331198, NCT03575351, NCT02631044, and NCT03483103.

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval regulations statutory provisions and 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 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 single arm clinical trial that includes a total of 50 treated patients to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as overall response rate and durability of the response with durable response based on a minimum follow-up of 15 months after first objective disease response.

Accelerated Approval Required Study

We remind you of your postmarketing requirement specified in your submission of March 13, 2024.

1. Conduct a single arm study of lisocabtagene maraleucel in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a prior Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor, to evaluate overall response rate and durability. The study must include a total of 50 treated patients and durable response should be based on a minimum follow-up of 15 months after first objective disease response.

    Final Protocol Submission: April 30, 2024

    Study/Trial Completion Date: March 31, 2027

    Final Report Submission: May 31, 2027

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of March 13, 2024.

Please submit the protocol(s) to your IND 16506 with a cross-reference letter to this BLA, STN BL 125714 explaining that these protocols were 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 required postmarketing clinical trial fail to verify that clinical benefit is conferred by lisocabtagene maraleucel, or are 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. 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) and 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, 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 your original BLA until all Postmarketing Requirements and 506B Commitments are fulfilled or released.

Please submit final study report as a supplement to this BLA, STN BL 125714. For administrative purposes, all submissions related to this postmarketing study

requirement must be clearly designated as "**Subpart E Postmarketing Study Requirements.**"

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 package insert labeling submitted under amendment 24, dated March 13, 2024.

This is a reminder that as of September 24, 2014, device constituents of combination products may be subject to certain provisions of the final Unique Device Identifier (UDI) rule. These provisions include the requirement to provide a UDI on the device constituent label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18 and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, please identify each device identifier implemented for the subject device constituent, and the device identifiers that have been discontinued for the subject device constituent as a labeling change in an annual report consistent with 21 CFR 601.12(f)(3). For more information on these requirements, please see the UDI website at http://www.fda.gov/udi.

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. 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.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels that are identical to the package and container labels submitted on March 13, 2024, 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 125714/205 at the time of use (prior to marketing) 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 available at http://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)).

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 a serious risk of secondary malignancies associated with use of lisocabtagene maraleucel.

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 study:

2. A post-marketing, multicenter, prospective, observational study to assess the long-term safety of lisocabtagene maraleucel and the risk of secondary malignancies occurring after treatment with lisocabtagene maraleucel. The study will include at least 300 subjects with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); the enrolled patients will be followed for 15 years after the product administration.

We acknowledge the timetable you submitted on February 14, 2024, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: May 31, 2024

Study Completion Date: June 30, 2044

Final Report Submission: June 30, 2045

Please submit the protocol to your IND 16506 with a cross-reference letter to this BLA, STN BL 125714 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.

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 125714. 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 BLA 125714 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.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for lisocabtagene maraleucel (BREYANZI) was originally approved on February 5, 2021, and the most recent REMS modification was approved on June 24, 2022. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that your approved REMS for BREYANZI must be modified to minimize the burden on the healthcare delivery system of complying with the REMS. Your approved REMS must be modified as follows:

- Modification to REMS goals: The goal for "Ensuring that those who prescribe, dispense, or administer BREYANZI are aware of how to manage the risks of CRS and neurological toxicities" is no longer necessary to ensure the benefits of the drug outweigh the risks and must be removed.
- Removal of requirement for educational and training materials: Patient Wallet Card, Live Training Program, and Knowledge Assessment.
- Removal of requirement to report any serious adverse events suggestive of cytokine release syndrome (CRS) or neurological toxicities to the REMS Program.

Your proposed modified REMS submitted March 13, 2024, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on February 5, 2021. The REMS assessment plan has been revised to remove education statistics to align with the above REMS modification. The REMS assessment plan must include, but is not limited to, the following:

For annual assessments:

The REMS Program Infrastructure and Performance (provide in tabular format as appropriate):

A. Hospitals and their associated clinics enrollment (provide for each reporting period and cumulatively)
   - List of all enrolled hospital sites, locations, dates of enrollment, and method (email, fax) of enrollment and dates of certification notification;
   - Number of incomplete enrollments at the time of assessment data lock.

B. Utilization of BREYANZI
   - Number of BREYANZI shipments sent to BREYANZI Certified Care Centers;
   - Number of unique patients treated with BREYANZI, stratified by BREYANZI Certified Care Center type; include age for treated patients;
   - Number and age of patients for which BREYANZI was ordered but never infused and the reason(s) that the patient was not treated
     - provide number of occurrences at each certified hospital for each reporting period and cumulatively;
   - Time between certification and first order for BREYANZI for each hospital certified during the assessment period.

C. Compliance with BREYANZI REMS
   - Number and name of non-certified hospital(s) that have treated a patient with BREYANZI and any corrective actions taken to prevent future occurrences (e.g., REMS hospital certification form) and the number of these that subsequently became certified (current reporting period and cumulative);
   - Audits: A summary of findings from first-order audits and annual audits (current reporting period) by type of audit deficiencies and stratified by type of center (i.e., clinic or hospital);
   - Summary report of all non-compliance, associated corrective and preventative actions (CAPA), and the status of CAPA plans.

D. BREYANZI REMS Customer Care Center
   - Number of contacts by stakeholder type (patient/guardian, prescriber, hospital and their associated clinic authorized representative, other health care provider (HCP), other) and reason for the call;
   - Summary of frequently asked questions (FAQ) by stakeholder type;
   - A description of each call, including stakeholder type, that may indicate an issue with access, burden, or an adverse event;
   - A summary of corrective actions resulting from issues identified;
   - Summary of any non-compliance that is identified through call center contacts, source of report and resulting corrective and preventative actions.

E. With respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified (Section 505-1(g)(3).

The requirements for assessments of an approved REMS under section 505-1(g)(3)

include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use: Provision of as many of the currently listed assessment plan items as is feasible.
f) If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS.
g) *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document,

with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125714 REMS ASSESSMENT METHODOLOGY

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 125714 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 125714
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125714
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125714
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125714
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR BLA 125714

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain

documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

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

Sincerely,

Lola Fashoyin-Aje, MD, MPH
Acting Director
Division of Clinical Evaluation Hematology
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and Research