Our STN: BL 125646/663

SUPPLEMENT APPROVAL
May 27, 2022

Novartis Pharmaceuticals Corporation
Attention: John Noh, PharmD
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Noh:

We have approved your request received August 27, 2021, to supplement your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for tisagenlecleucel, to add a new indication for the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy, and to include a major modification to the approved Risk Evaluation and Mitigation Strategy (REMS), according to [21 CFR 601.41].

The review of this supplement was associated with the following National Clinical Trial (NCT) number: 03568461.

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval regulations, we may consider 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 regulations requires, among other things, that you conduct an adequate and well-controlled clinical trial to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as favorable progression-free survival demonstrated in a randomized clinical trial comparing tisagenlecleucel to the standard of care.

Accelerated Approval Required Studies

We remind you of your postmarketing requirement specified in your submissions of March 4, 2022, and May 20, 2022.

1. Conduct a randomized phase 3 trial in adult patients with relapsed or refractory follicular lymphoma. Patients will be randomized to tisagenlecleucel or an investigator's choice of regimens consistent with the standard of care. The primary endpoint will be progression-free survival with secondary endpoints that include overall survival and objective response rate.

   Final Protocol Submission: December 31, 2022
   Study/Trial Completion: March 31, 2028
   Final Report Submission: September 30, 2028

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letters of March 4, 2022, and May 20, 2022.

You must conduct this study with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by tisagenlecleucel, 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 protocol to your IND 16130 with a cross-reference letter to BLA STN BL 125646 explaining that this protocol was submitted to the IND. Please refer to the sequential number for this study and the submission number as shown in this letter.

Your postmarketing requirement study in consideration for an accelerated approval is 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 BLA until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released.

Please submit the final study report as an efficacy supplement to BLA 125646. 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 submitted under amendment 46 on May 25, 2022.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the Package Insert, submitted on May 25, 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.

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

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125646 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)).

Please submit an amendment to all pending supplemental applications for this BLA that include revised labeling incorporating a revised content of labeling that includes these changes.

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 and since this is a supplemental BLA, 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 tisagenlecleucel in adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

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

2. A post marketing, prospective, multi-center, observational study to assess the long-term safety of tisagenlecleucel and the risk of secondary malignancies occurring after treatment with tisagenlecleucel. The study will include at least 300 adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy; the enrolled patients will be followed for 15 years after product administration.

   We acknowledge the timetable you submitted on April 7, 2022, which states that you will conduct this study, according to the following schedule:

Final Protocol Submission: September 30, 2022
Study Completion Date: September 30, 2042
Final Report Submission: September 30, 2043

Please submit the protocol(s) to your IND 16130, with a cross-reference letter to BLA STN BL 125646 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 BLA STN BL 125646. 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 STN BL 125646 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 correspondence of April 7, 2022, as outlined below:

3. Novartis Pharmaceuticals Corporation commits to submit a Prior Approval Supplement with revised Percentage of Viable T cells lot release criterion in alignment with the demonstrated tisagenlecleucel commercial manufacturing capability.

   Final Report Submission: July 31, 2022

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125646. 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**.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for tisagenlecleucel (KYMRIAH) was originally approved on August 30, 2017. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS consists of changes to the REMS Patient Wallet Card, Live Training Program, Knowledge Assessment, and REMS Program Website to align with labeling changes related to the new indication.

Your proposed modified REMS, submitted on May 5, 2022, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on August 30, 2017. There are no changes to the REMS assessment plan described in our August 30, 2017, letter.

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 a 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 a REMS modification*, 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 125646 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 125646 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 125646
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125646
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION
or

NEW SUPPLEMENT FOR BLA 125646
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125646
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 125646

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.

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).
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,

Tejashri Purohit-Sheth, MD
Director
Division of Clinical Evaluation and
Pharmacology/Toxicology
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research