NDA 213246

ACCELERATED APPROVAL

Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company
Attention: Elaine Fashana
Executive Director, Regulatory Affairs
701 Gateway Boulevard, Suite 420
South San Francisco, CA 94062

Dear Ms. Fashana:

Please refer to your new drug application (NDA), received December 4, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Retevmo (selpercatinib) capsules.

This new drug application provides for the use of Retevmo (selpercatinib) capsules for the following indications:

- Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC);

- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy;

- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR 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, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert). 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.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on April 7, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 213246**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the provided stability data, an 18-month expiration dating period is granted for the 40 mg and 80 mg Retevmo (selpercatinib) capsules when stored in the original container at 20 ºC to 25ºC (68 ºF to 77ºF); excursions permitted to 15 ºC to 30ºC (59 ºF to 86ºF) [see USP Controlled Room Temperature].

ADVISORY COMMITTEE

Your application for Retevmo (selpercatinib) capsules was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues in the intended population, and there were no controversial issues that would benefit from advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirements specified in your submission dated April 22, 2020. These requirements, along with required completion dates, are listed below.

3829-1 Submit the final report including datasets from a multi-center, randomized trial comparing selpercatinib to physician's choice of approved therapies in patients with kinase inhibitor-naïve, progressive, advanced or metastatic RET-mutant medullary thyroid cancer to confirm clinical benefit of selpercatinib with progression-free survival as a key secondary end point- as assessed by blinded independent central review.

The timetable you submitted on April 22, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2019 (completed)
Trial Completion:	04/2026
Final Report Submission:	10/2026

3829-2 Submit a final report including datasets from an ongoing clinical trial to verify and further characterize the clinical benefit of selpercatinib for the treatment of patients with 1) treatment-naïve RET fusion-positive NSCLC and with 2) RET fusion-positive NSCLC who have previously received platinum chemotherapy that will provide a more precise estimation of the BICR-assessed overall response rate and duration of response after all responders in the population of at least 65 patients have been followed for at least 12 months from the date of initial response (or until disease progression, whichever comes first) in patients with treatment-naïve NSCLC and after all responders have been followed for at least 6 months in the population of patients (at least 180 patients) with NSCLC previously treated with platinum therapy.

The timetable you submitted on April 22, 2020, states that you will conduct this trial according to the following schedule:

Trial Completion:	05/2021
Final Report Submission:	11/2021

3829-3 Submit a final report including datasets, to verify and further characterize the clinical benefit of selpercatinib for the treatment of patients with RET fusion-positive thyroid cancer who have received radioactive iodine (if appropriate for their tumor histology) to provide a more precise estimation of the BICR-assessed overall response rate and duration of response in at least 50 patients after all responding patients have been followed for 12 months following onset of response or until disease progression, whichever comes first.

The timetable you submitted on April 22, 2020, states that you will conduct this trial according to the following schedule:

Trial Completion:	06/2023
Final Report Submission:	12/2023

Submit clinical protocols to your IND 133193 (or 144696, as appropriate) for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 this drug product for these indications have orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the potential for the unexpected serious risks of selpercatinib on the growth and development of adolescent patients and the potential for the unexpected serious risk of carcinogenicity.

Furthermore, the active post-market risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

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

3829-4 Submit the final report, of an integrated safety analysis from clinical studies that further characterize the potential serious risk of long-term adverse effects of selpercatinib on growth and development, including an assessment of growth plate abnormalities in a sufficient number of adolescent patients 12 years of age and older with RET mutant MTC and RET fusion-positive thyroid cancer. Patients will be monitored for growth and development using age-appropriate screening tools. Evaluations will include growth as measured by height, weight, height velocity and height standard deviation scores, age at adrenarche if applicable (males), age at menarche if applicable (females) and Tanner stage. Patient monitoring will be performed until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first. Include the datasets with the final report. The results from this report may inform labeling.

The timetable you submitted on April 22, 2020, states that you will conduct this trial according to the following schedule:

Trial Completion:	06/2025
Final Report Submission:	12/2025

3829-5 Conduct a rodent carcinogenicity study in mice to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment prior to initiating the study.

The timetable you submitted on April 22, 2020, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 01/2021
Final Protocol Submission: 05/2021
Trial Completion: 11/2021
Final Report Submission: 10/2022

3829-6 Conduct a rodent carcinogenicity study in rats to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment prior to initiating the study.

The timetable you submitted on April 22, 2020, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 01/2021
Final Protocol Submission: 05/2021
Trial Completion: 05/2023
Final Report Submission: 04/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify a serious risk of drug toxicity in patients with hepatic and renal impairment and to identify a potential drug interaction resulting in lower/higher drug exposure and resultant serious risks from the effects of selpercatinib on the pharmacokinetics of P-gp substrates.

3829-7 Submit the analysis and datasets with the final report from an ongoing hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of selpercatinib in patients with normal hepatic function and patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*."

The timetable you submitted on April 22, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 10/2018 (completed)
Trial Completion: 10/2019 (completed)
Final Report Submission: 06/2020

3829-8 Submit the analysis and datasets with the final report from an ongoing renal impairment clinical trial to evaluate the pharmacokinetics and safety of selpercatinib in patients with normal renal function and patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry titled "*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*."

The timetable you submitted on April 22, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 11/2018 (completed)
Trial Completion: 11/2019 (completed)
Final Report Submission: 07/2020

3829-9 Submit the final report and datasets from a clinical drug-drug interaction study to evaluate the effect of selpercatinib on the pharmacokinetics of a P-gp substrate,and inform appropriate management strategies for clinically relevant drug interactions. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: "*Clinical Drug Interaction Studies - Cytochrome P450 Enzyme and Transporter-Mediated Drug Interactions*."

The timetable you submitted on April 22, 2020, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 09/2020
Final Protocol Submission: 12/2020
Trial Completion: 08/2021
Final Report Submission: 11/2021

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocols to your IND 133193 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 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. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 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 submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3829-10 Submit the final report of an analytical and clinical validation study, using clinical trial data, that is adequate to support labeling of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of selpercatinib for patients with RET gene fusions in non-small cell lung cancer. The results of the validation study may inform product labeling.

The timetable you submitted on May 1, 2020, states that you will conduct this study according to the following schedule:

PMA Submission: 12/2021
Final Report Submission: 12/2021

3829-11 Submit the final report of an analytical and clinical validation study, using clinical trial data, that is adequate to support labeling of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of selpercatinib for patients with RET gene fusion-positive thyroid cancer and RET mutation-positive medullary thyroid cancer. The results of the validation study may inform product labeling.

The timetable you submitted on May 1, 2020, states that you will conduct this study according to the following schedule:

PMA Submission: 05/2022
Final Report Submission: 05/2022

Submit all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated

references, and approved Prescribing Information (PI)/Medication Guide/Patient Package Insert (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

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.*[5]

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[6]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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, call the Regulatory Project Manager for this application.

If you have any questions, call Autumn Zack-Taylor, M.S., Regulatory Health Project Manager, at (240) 402-5913.

Sincerely,

{See appended electronic signature page}

Marc Theoret, M.D.
Acting Deputy Director
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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