



NDA 213246/S-012

ACCELERATED APPROVAL

Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company
Attention: Viktoriya Ilaria
Senior Director, Global Regulatory Affairs - North America
Lily Corporate Center, Drop Code 2543
Indianapolis, IN 46285

Dear Viktoriya Ilaria:

Please refer to your supplemental new drug application (sNDA) dated December 13, 2023, received December 13, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Retevmo (selpercatinib) capsules.

This “Prior Approval” sNDA supports approval for the use of selpercatinib in pediatric patients 2 years of age and older with *RET*-activated solid tumors and to include interim efficacy and safety results from Study LIBRETTO-121 in the US Product Insert (USPI).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 314.510, 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 accelerated approval statutory provisions and regulations.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 314.510 you are required to conduct further adequate and well-controlled studies intended to verify and describe clinical benefit. You are required to conduct such studies with due diligence. If required postmarketing studies fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement(s) specified in your submission dated May 24, 2024. These requirements are listed below.

- 4639-1 Complete the primary analysis for a multi-center, randomized trial (LIBRETTO-531) comparing selpercatinib to physician's choice of approved therapies in patients with kinase inhibitor-naïve, progressive, advanced or metastatic RET-mutant medullary thyroid cancer intended to confirm clinical benefit of selpercatinib with progression-free survival as a primary endpoint as assessed by blinded independent central review.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

The timetable you submitted on May 24, 2024, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 07/2019 (completed)

Trial Completion: 05/2023 (completed)

Final Report Submission: 03/2024 (submitted)

- 4639-2 Complete analyses intended 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) in a single-arm clinical trial (LIBRETTO-001) 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 May 24, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion: 01/2023 (completed)

Final Report Submission: 08/2023 (submitted)

- 4639-3 Complete clinical trial(s) to obtain data on the clinical efficacy of selpercatinib through more precise estimation of the overall response rate and mature response duration per independent review assessment, in at least 60 patients with locally advanced or metastatic RET-fusion positive solid tumors other than non-small cell lung cancer and thyroid cancer, who have progressed on prior systemic treatment or have no satisfactory alternative treatment options. A sufficient number of patients with tumor types for which responses require additional characterization (e.g., colorectal cancer, esophagogastric cancer, and glioma) will be evaluated. Overall response rate and duration of response will be assessed by independent central review and all responding patients will be followed for at least 12 months following the onset of response or until disease progression or death or early treatment discontinuation, whichever comes first. Include available data regarding RET fusion partners and co-occurring genetic alterations for all patients.

The timetable you submitted on May 24, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion: 06/2025

Final Report Submission: 12/2025

Submit clinical protocols to your IND 133193 for this product. 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.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this NDA approximately every 180 days (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 section 506(c). One report will be a standalone submission and the other report will be combined with your application’s annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 314.81(b)(2). The standalone 180-day report will be due 180 days after the date of approval of the original NDA (with a 60-day grace period). Submit the other 180-day report with your application’s ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.³ Depending on the date of approval of the original application, you may be required to submit a 180-day report shortly after receipt of this letter.

Your 180-day reports must include the information listed in 21 CFR 314.81(b)(2)(vii)(a). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics*, to submit your 180-day reports.⁴

180-day reports must be clearly designated “**NDA 213246/S-012 180-Day AA PMR Progress Report.**”

FDA will consider the submission of your application’s ASR under section 506B(a)(1) and 21 CFR 314.81(b)(2), in addition to the submission of reports 180 days after the date of approval of the original NDA each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this NDA as a supplemental application. For administrative purposes, the cover page of 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

³ You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) 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.

⁴ 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>.

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 this indication has an 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 assess the known serious risk of long-term adverse effects of selpercatinib on growth and development of pediatric patients, including but not limited to growth plate abnormalities.

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

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the serious risk.

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

- 4639-4 Conduct comprehensive safety analyses from clinical studies that further characterize the known serious risk of long-term adverse effects of selpercatinib on growth and development, including but not limited to growth plate abnormalities, in a sufficient number of pediatric patients with *RET*-altered solid tumors ages 2 to < 12 years of age. Monitor patients for growth and development using age-appropriate screening tools. Include evaluations of growth as measured by height, weight, height velocity and height standard deviation scores, age at menarche if applicable (females) and Tanner stage. Monitor patients until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.

The timetable you submitted on May 24, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion: 06/2029
Final Report Submission: 12/2029

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.⁵

Submit clinical protocol(s) to your IND 142299 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) 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(a)(1) 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(a)(1) 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.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

⁵ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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 (301) 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, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁶

REPORTING REQUIREMENTS

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

If you have any questions, contact Tselaine Jones Smith, Regulatory Project Manager, via email at Tselaine.JonesSmith@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nicole Drezner, MD
Deputy Division Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

⁶ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert

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/

NICOLE L DREZNER
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