NDA 213246/S-011
NDA 213246/S-013

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING REQUIREMENTS

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

Dear Michael P. Roesner:

Please refer to the following supplemental new drug applications (sNDA) listed below, and its amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Retevmo (selpercatinib) capsules:

- *Prior Approval sNDA 011*, dated and received on November 29, 2023, which provides for updates to the Retevmo (selpercatinib) U.S. Prescribing Information labeling to include interim efficacy and safety results from the LIBRETTO-431 study; and

- *Prior Approval sNDA 013*, dated and received on March 28, 2024, which provides for fulfillment of Postmarketing Requirements (PMRs) 3892-1 and 3892-6, and conversion from accelerated approval to traditional approval of Retevmo (selpercatinib) for the treatment of adult and pediatric patients 2 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy.

APPROVAL & LABELING

We have completed our review of these applications, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 Effected" (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).

SUBPART H FULFILLED

We approved sNDA 213246/S-013 under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 314.510.

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

[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.

exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submission dated March 28, 2024, containing the final reports for the following postmarketing requirements listed in the May 8, 2020, and May 29, 2024, approval letters.

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.

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

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.

We have reviewed your submission and conclude that the above requirements were fulfilled.

We remind you that there are postmarketing requirements listed in the May 8, 2020, and May 29, 2024, approval letters that are still open.

We remind you that accelerated approval PMRs 4639-2 and 4639-3 listed in the May 29, 2024, approval letter are still open. Pursuant to 21 CFR 314.510 (Subpart H), continued approval of the drug is contingent upon verification and description of clinical benefit and completion of the clinical trial for PMRs 4639-2 and 4639-3.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

For NDA 213246/S-013

4697-1 Complete survival follow-up of patients in the LIBRETTO-531 trial at 125 deaths or 6 years from randomization of the first patient, whichever occurs first, to further characterize the efficacy and clinical benefit of selpercatinib in patients with advanced or metastatic *RET* mutant medullary thyroid cancer who are naïve to tyrosine kinase inhibitors.

The timetable you submitted on August 23, 2024, states that you will conduct this study according to the following schedule:

Trial Completion:	03/2026
Final Report Submission:	09/2026

For NDA 213246/S-011

4714-1 Complete survival follow-up of patients in the LIBRETTO-431 trial at 175 deaths to further characterize the efficacy and clinical benefit of selpercatinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *RET* gene fusion.

The timetable you submitted on September 26, 2024, states that you will conduct this study according to the following schedule:

Trial Completion:	09/2033
Final Report Submission:	03/2034

Submit clinical protocols to your IND 144696 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and 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/subjects 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

You may request advisory comments on proposed introductory advertising and promotional labeling. 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.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

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).

REPORTING REQUIREMENTS

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

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, email Maritsa Stephenson, Regulatory Health Project Manager, at maritsa.stephenson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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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