NDA 216059

**CORRECTED ACCELERATED APPROVAL**

Loxo Oncology, Inc.
Attention: Lars Holzhausen, PhD, RAC
Associate Vice President, Regulatory Affairs
201 Haskins Way, Suite 400
South San Francisco, CA 94080

Dear Dr. Holzhausen:

Please refer to your new drug application (NDA) dated and received May 27, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jaypirca (pirtobrutinib) tablets.

We also refer to our approval letter dated January 27, 2023, which contained the following error: Incorrect version of the Prescribing Information and Patient Package Insert.

This corrected action letter incorporates the correction of the error. The effective date will remain January 27, 2023, the date of the original letter.

This NDA provides for the use of Jaypirca (pirtobrutinib) tablets for the treatment of adult patients with relapsed or refractory mantle cell lymphoma after at least two lines of systemic therapy, including a BTK inhibitor.

## 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 Prescribing Information, text for 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 submitted on December 22, 2022, 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 216059**." Approval of this submission by FDA is not required before the labeling is used.

## DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Jaypirca (pirtobrutinib) tablets shall be 24 months from the date of manufacture when stored at 20°C to 25°C.

## ADVISORY COMMITTEE

Your application for Jaypirca was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

## ACCELERATED APPROVAL REQUIREMENTS

Products approved under accelerated approval pursuant to section 506(c) of the FDCA and 21 CFR 314.510, may require further adequate and well-controlled clinical trials

[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.

intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated December 12, 2022. This requirement, along with required completion dates, is listed below.

4389-1 Complete a randomized clinical trial to obtain data on the clinical efficacy and safety of pirtobrutinib in patients with mantle cell lymphoma. The trial should compare pirtobrutinib monotherapy to an investigator's choice of approved BTK inhibitors in patients with mantle cell lymphoma. The primary endpoint should be progression-free survival as assessed by an independent review committee, with secondary endpoints that include overall survival and objective response rate. The trial should enroll a sufficiently representative study population to reflect the racial and ethnic diversity of the U.S. patient population with mantle cell lymphoma and allow for interpretation of the results in these patient populations.

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| Final Protocol Submission: | 01/2021 |
| Trial Completion: | 06/2026 |
| Final Report Submission: | 12/2026 |

Submit clinical protocols to your IND 139876 for this product. In addition, you must submit status reports of the progress of each requirement not later than 180 days after the date of approval of this drug and every 180 days thereafter (section 506(B)(a) of the FDCA as amended by section 3210(b) of the Food and Drug Omnibus Reform Act of 2022). 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 the 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 subjects 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 this indication has an orphan drug designation and the molecular target of your drug is not relevant to the growth or progression of a pediatric cancer, 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 known serious risks of serious infections, cardiac arrhythmias, bleeding, cytopenias, and second primary malignancies.

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 these serious risks.

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

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

4389-2 Conduct a study to characterize the longer-term safety of pirtobrutinib monotherapy, at a planned dose of 200 mg daily, in patients with hematologic malignancies treated in Study 18001. Characterize safety and exposure with a minimum of 24 months of follow-up. Include evaluations, supplemented by narratives, of deaths in the absence of treated progressive disease, serious adverse reactions, adverse reactions of special interest (including but not limited to serious infections, cardiac arrhythmias, bleeding, cytopenias, and second primary malignancies), and treatment discontinuations for reasons other than progressive disease.

The timetable you submitted on December 12, 2022, states that you will conduct this trial according to the following schedule:

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| Final Protocol Submission (Analysis Plan): | 04/2023 |
| Trial Completion: | 03/2025 |
| Final Report Submission: | 09/2025 |

4389-3 Conduct an integrated safety analysis of patients with hematologic malignancies treated with pirtobrutinib monotherapy at the 200 mg daily dose in clinical trials and from post-marketing reports to further

characterize the risk of second primary malignancies with extended follow-up. Patients enrolled in clinical trials should have 5 years minimum follow-up for development of second primary malignancies. Include evaluations of incidence rates, types, severity, time to onset, potential predisposing factors, and outcomes.

The timetable you submitted on December 12, 2022, states that you will conduct this trial according to the following schedule:

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| Draft Protocol Submission (Analysis Plan): | 04/2023 |
| Final Protocol Submission (Analysis Plan): | 07/2023 |
| Interim Report: | 09/2025 |
| Study Completion: | 12/2027 |
| Final Report Submission: | 06/2028 |

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]

Submit clinical protocol(s) to your IND 139876 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 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.

[3] 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*.[4]

## REPORTING REQUIREMENTS

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

## POST APPROVAL FEEDBACK MEETING

New molecular entities 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.

[4] https://www.fda.gov/media/128163/download.

If you have any questions, call, Denise Felluca, Regulatory Project Manager, at 301-796-4574 or denise.felluca@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Marc Theoret, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

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

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**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.**

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