



NDA 215310

ACCELERATED APPROVAL

Takeda Pharmaceuticals USA, Inc.
Attention: Julie Dixon, Ph.D.
Vice President, Head of Global Regulatory Affairs Oncology
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Dixon:

Please refer to your new drug application (NDA) dated February 26, 2021, received February 26, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EXKIVITY (mobocertinib) capsules.

This NDA provides for the use of EXKIVITY (mobocertinib) capsules for treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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, text for the 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

We acknowledge your August 9, 2021, submission containing final printed container labeling.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for EXKIVITY (mobocertinib) capsules shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

ADVISORY COMMITTEE

Your application for EXKIVITY was not referred to an FDA advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

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 requirement specified in your submission dated September 10, 2021. This requirement, along with required completion dates, is listed below.

- 4148-1 Conduct a multicenter, randomized clinical trial and submit the final progression-free survival (PFS) results that verify and describe the clinical benefit of mobocertinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors harbor epidermal growth factor receptor (EGFR) exon 20 insertion mutations.

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>.

Final Protocol Submission: 01/2021

Trial Completion: 09/2023

Final Report Submission: 03/2024

Submit clinical protocols to your IND 126721 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.

We are waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable as NSCLC does not occur in children and due to the extreme rarity of EGFR exon 20 insertion mutations in pediatric cancers.

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 a known serious risk of QT prolongation, ventricular arrhythmia, Torsades de Pointes, and cardiac toxicity in patients receiving EXKIVITY (mobocertinib).

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.

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

- 4148-2 Conduct an integrated safety analysis containing data from randomized clinical trials to further characterize the known serious signal of QT prolongation, ventricular arrhythmia and Torsades de Pointes. The analyses should include assessment and collection of data to describe the incidence, clinical presentation, management, and outcome of events comprising the Torsades de Pointes SMQ as well as other major adverse cardiovascular events; including arrhythmias, fatal cardiovascular adverse events, and events of sudden death. Detailed narratives of such cases should be included in the final report.

The timetable you submitted on September 10, 2021, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission:	09/2022
Final Analysis Plan Submission:	08/2023
Study Completion:	09/2023
Final Report Submission:	03/2024

- 4148-3 Conduct an integrated safety analysis of data from randomized clinical trials to further characterize the known serious signal of cardiac failure. The analyses should include an assessment of data including left ventricular ejection fraction monitoring to describe the incidence, clinical presentation, management, and outcome of events comprising the cardiac failure and cardiomyopathy standardized MedDRA queries (SMQs) including events of decreased ejection fraction. Detailed narratives of such cases should be included in the final report.

The timetable you submitted on September 10, 2021, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission:	09/2022
Final Analysis Plan Submission:	08/2023
Study Completion:	09/2023
Final Report Submission:	03/2024

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

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>.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of increased adverse reactions when EXKIVITY (mobocertinib) is administered in patients with severe renal impairment, moderate and severe hepatic impairment and to determine appropriate dose adjustment when mobocertinib is used concomitantly with BCRP substrates.

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

- 4148-4 Conduct a renal impairment clinical trial to evaluate the pharmacokinetics and safety of mobocertinib in patients with normal renal function and patients with severe renal impairment. Design and conduct the trial in accordance with the FDA Draft Guidance for Industry titled: ["Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing."](#)

The timetable you submitted on September 10, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2020
Trial Completion:	09/2022
Final Report Submission:	03/2023

Submit the analysis and datasets with the final report.

- 4148-5 Conduct a hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of mobocertinib in patients with normal hepatic function and patients with moderate and severe 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 September 10, 2021 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2020
Trial Completion:	06/2022
Final Report Submission:	12/2022

Submit the analysis and datasets with the final report.

- 4148-6 Conduct a study to assess the effect of mobocertinib and its active metabolites on the pharmacokinetics of a breast cancer resistance protein

(BCRP) substrate to determine appropriate dosage recommendations when mobocertinib is administered concomitantly with BCRP substrates. Design and conduct the study in accordance with the FDA Guidances for Industry titled "[Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions](#)," and "[Physiologically Based Pharmacokinetic Analyses - Format and Content](#)".

The timetable you submitted on September 10, 2021 states that you will conduct this trial according to the following schedule:

Draft Analysis Plan Submission:	10/2021
Final Analysis Plan Submission:	12/2021
Study Completion:	04/2022
Final Report Submission:	05/2022

Submit the analysis and datasets with the final report.

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 protocol(s) to your IND 126721 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

⁴ 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>.

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 commitment:

- 4148-7 Conduct an analysis containing data from clinical trials enrolling a sufficient representation of U.S. racial and ethnic minorities, including Black or African American patients, that is reflective of the U.S. population of patients with EGFR exon 20 insertion-mutated NSCLC to further characterize the safety and efficacy of mobocertinib in Black or African American patients with EGFR exon 20 insertion-mutated NSCLC.

The timetable you submitted on September 10, 2021, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission:	09/2022
Final Analysis Plan Submission:	08/2023
Study Completion:	09/2023
Final Report Submission:	03/2024

Submit clinical protocols to your IND 126721 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 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 314.55, 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 314.55, 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*.⁵

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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.

⁵ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

If you have any questions, call Jacqueline Glen, Regulatory Health Project Manager, at (240) 402-9558.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Deputy Office Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - o Prescribing Information
 - o Patient Package Insert
- 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/

JULIA A BEAVER
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