NDA 216340

ACCELERATED APPROVAL

Mirati Therapeutics, Inc.
Attention: Vincent Caralli
Executive Director, Regulatory Affairs
3545 Cray Court
San Diego, CA 92121

Dear Mr. Caralli:

Please refer to your new drug application (NDA) dated December 14, 2021, received December 14, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Krazati (adagrasib) oral tablets.

This NDA provides for the use of for Krazati (adagrasib) oral tablets for treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA approved test, who have received at least one prior systemic therapy.

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.

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 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]

[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 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 carton and container labeling submitted on June 8, 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 216340**." 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 Krazati (adagrasib) oral tablet shall be 18 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).

ADVISORY COMMITTEE

Your application for KRAZATI was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues in the intended population.

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 November 28, 2022. This requirement, along with required completion dates, is listed below.

4378-1 Conduct a randomized comparative clinical trial of adagrasib in adult patients with KRAS G12C mutated, locally advanced or metastatic NSCLC who have received at least one prior systemic therapy, to obtain overall survival, progression free survival, overall response rate, and duration of response. This data may be obtained from the ongoing clinical trial entitled, "A Randomized Phase 3 Study of MRTX849 versus Docetaxel in Patients with Previously Treated Non-Small Cell Lung Cancer with KRAS G12C Mutation."

Final Protocol Submission:	12/2022
Trial Completion:	06/2025
Final Report Submission:	12/2025

Submit clinical protocols to your IND 152385 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 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, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 gastrointestinal toxicity, and to identify unexpected serious risks of drug toxicity due to the potential for elevated drug levels from concomitant drug use of strong CYP2C8 inhibitors, and BCRP inhibitors, and to determine the appropriate dose adjustment when adagrasib is used concomitantly with sensitive CYP2B6 substrates, and probe MATE-1/-2K substrates.

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 a known serious risk or identify unexpected serious risks.

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

4378-2 Conduct a multicenter, randomized clinical trial to further characterize serious adverse events, including gastrointestinal toxicity, and compare the safety of adagrasib 600 mg twice daily versus an alternative daily dosage in patients with locally advanced or metastatic, KRAS G12C mutated, non-small cell lung cancer who have received at least one prior systemic therapy. Include a comparative analysis of dose- and exposure-response relationships for safety including further characterization of the rates of Grade ≥3 adverse reactions, serious adverse reactions, and dose reductions, interruptions, and discontinuations due to adverse reactions. Additionally, conduct efficacy analyses including a comparative analysis of dose- and exposure-response relationships for efficacy for the two dosing regimens. Incorporate systematically assessed patient-reported outcome assessments to evaluate tolerability and conduct exploratory exposure response analyses.

The timetable you submitted on November 28, 2022, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	10/2022 (completed)
Study Completion:	06/2025
Final Report Submission:	10/2025

Submit the datasets with the final report submission.

4378-3 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeated doses of a strong CYP2C8 inhibitor on the steady-state pharmacokinetics of adagrasib. Refer to the following FDA Guidance for Industry for additional details: “Clinical Drug Interaction Studies-Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.”

The timetable you submitted on November 28, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	02/2023
Final Protocol Submission:	04/2023

Study Completion:	08/2023
Final Report Submission:	03/2024

4378-4 Conduct a clinical pharmacokinetic trial to evaluate the effect of a BCRP inhibitor on the single-dose pharmacokinetics of adagrasib. Refer to the following FDA Guidance for Industry for additional details: "Clinical Drug Interaction Studies-Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on November 28, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2023
Final Protocol Submission:	05/2023
Study Completion:	09/2023
Final Report Submission:	04/2024

4378-5 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeated doses of adagrasib (at steady-state) on the single dose pharmacokinetics of a sensitive CYP2B6 substrate. Refer to the following FDA Guidance for Industry for additional details: "Clinical Drug Interaction Studies-Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on November 28, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	04/2023
Final Protocol Submission:	06/2023
Study Completion:	10/2023
Final Report Submission:	05/2024

4378-6 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeated doses of adagrasib (at steady-state) on the single dose pharmacokinetics of a probe MATE-1/-2K substrate. Refer to the following FDA Guidance for Industry for additional details: "Clinical Drug Interaction Studies-Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on November 28, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	05/2023
Final Protocol Submission:	07/2023
Study Completion:	11/2023
Final Report Submission:	06/2024

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]

Submit clinical protocol(s) to your IND 152385 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.

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

[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.

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.

If you have any questions, call Opeyemi Udoka, D.P.T, Regulatory Project Manager at (240) 402-4558 or email opeyemi.udoka@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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

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/

RICHARD PAZDUR
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