NDA 211723

ACCELERATED APPROVAL

Epizyme, Inc.
Attention: Huiping Jiang, Ph.D.
Vice President, Regulatory Affairs
400 Technology Square, 4th Floor
Cambridge, MA 02139

Dear Dr. Jiang:

Please refer to your new drug application (NDA) received May 23, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for TAZVERIK (tazemetostat) tablets, 200 mg.

This new drug application provides for the use of TAZVERIK (tazemetostat) tablets, 200 mg for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.

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.

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 Medication Guide). 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.

[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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on January 13, 2020, 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 211723."** Approval of this submission by FDA is not required before the labeling is used.

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 requirements specified in your submissions dated January 16, 2020 and January 23, 2020. These requirements, along with required completion dates, are listed below.

3787-1 Submit the final results from a confirmatory randomized trial in patients with epithelioid sarcoma to confirm clinical benefit and provide additional efficacy data that may inform product labeling for tazemetostat.

Draft Protocol Submission:	07/2019 (completed)
Final Protocol Submission:	09/2019 (completed)
Trial Completion:	03/2029
Final Report Submission:	09/2029

3787-2 Submit the final report and datasets for the final analysis of overall response rate and duration of response for clinical trial EZH-202 titled, "A Phase II, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects With INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma" to verify and confirm clinical benefit of tazemetostat, that may inform product labeling. An additional 25 patients from Cohort 6 beyond those included in the original NDA submission will be evaluated and all responding patients will be followed for at least 12 months from the onset of response.

Draft Protocol Submission,:	03/2020
Final Protocol Submission:	05/2020

Trial Completion:	12/2022
Final Report Submission:	06/2023

Submit clinical protocols to your IND 124608 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.

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 a known serious risk of acute myeloid leukemia, myelodysplastic syndrome, T-lymphoblastic lymphoma, and other secondary malignancies in patients receiving tazemetostat.

Furthermore, the new pharmacovigilance system that FDA is required to establish 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 study:

3787-3 Conduct cumulative, integrated safety analyses after 5 and 10 years of follow-up from an adequate number of patients enrolled in clinical trials to characterize the risk of acute myeloid leukemia, myelodysplastic syndrome, T-lymphoblastic lymphoma, and other secondary malignancies in patients receiving TAZVERIK; include incidence rates, time to onset, predisposing factors, and outcomes. These safety evaluations will be adequate to inform labeling of patient populations at highest risk and to provide evidence-based monitoring recommendations.

The timetable you submitted on January 17, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2019 (completed)
Final Protocol Submission:	09/2019 (completed)
Study Completion:	03/2029
Interim (5 year) Report Submission:	03/2025
Final (10 year) Report Submission:	03/2030

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks of elevated drug levels in the presence of moderate or severe hepatic impairment, and to determine appropriate dose adjustment when tazemetostat is used concomitantly with strong CYP3A inhibitors.

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

3787-4 Conduct a pharmacokinetic and safety study in cancer patients with moderate or severe hepatic impairment investigating the effects of hepatic impairment (based on the NCI Organ Dysfunction Working Group (ODWG) criteria) on the repeat dose pharmacokinetics of tazemetostat compared to cancer patients with normal hepatic function. This study will assess the magnitude of increased tazemetostat exposure and determine appropriate dosing recommendations of tazemetostat for patients with moderate or severe hepatic impairment.

The timetable you submitted on January 16, 2020, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	08/2019 (completed)
Final Protocol Submission:	01/2020
Trial Completion:	07/2022
Final Report Submission:	01/2023

3787-5 Conduct a cross-over study in patients with cancer investigating the effects of itraconazole, a strong CYP3A inhibitor, on the repeat dose pharmacokinetics of tazemetostat to assess the magnitude of increased tazemetostat exposure and to determine appropriate dosing recommendations for tazemetostat when it is administered concomitantly with strong CYP3A inhibitors.

The timetable you submitted on January 16, 2020 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	06/2020
Final Protocol Submission:	09/2020
Trial Completion:	12/2022
Final Report Submission:	06/2023

Submit clinical protocols to your IND 124608 with a cross-reference letter to this NDA 211723. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3787-6 Conduct a cross-over study in patients with cancer investigating the effects of rifampin, a strong CYP3A inducer, on the repeat dose

pharmacokinetics of tazemetostat to assess the magnitude of decreased tazemetostat exposure and to determine appropriate dosing recommendations for tazemetostat when it is administered concomitantly with strong CYP3A inducers.

The timetable you submitted on January 16, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2020
Final Protocol Submission:	09/2020
Trial Completion:	12/2022
Final Report Submission:	06/2023

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 124608 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 314.550, 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 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 (PI)/Medication Guide/Patient Package Insert (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[4]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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.

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, call Kristin Jarrell, Regulatory Health Project Manager, at (301) 796-0137.

Sincerely,

{See appended electronic signature page}

Marc Theoret, M.D.
Deputy Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and 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/

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