

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211723Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 10, 2020
Requesting Office or Division: Division of Oncology 3 (DO3)
Application Type and Number: NDA 211723
Product Name and Strength: Tazverik (tazemetostat) Tablets, 200 mg
Applicant/Sponsor Name: Epizyme Inc.
OSE RCM #: 2019-1113-2
DMEPA Safety Evaluator: Janine Stewart, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label received on December 27, 2019 for Tazverik. Division of Oncology 3 (DO3) requested that we review the revised container label for Tazverik (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review memorandum.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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^a Stewart J. Label and Labeling Review Memorandum for Tazverik (NDA 211723). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 10. RCM No.: 2019-1113-1.

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/s/

JANINE A STEWART
01/10/2020 04:03:06 PM

CHI-MING TU
01/10/2020 04:05:02 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 10, 2019
Requesting Office or Division: Division of Oncology 3 (DO3)
Application Type and Number: NDA 211723
Product Name and Strength: Tazverik (tazemetostat) Tablets, 200 mg
Applicant/Sponsor Name: Epizyme Inc.
OSE RCM #: 2019-1113-1
DMEPA Safety Evaluator: Janine Stewart, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1 PURPOSE OF MEMORANDUM

We previously evaluated proposed container label received on August 22, 2019 for Tazemetostat Tablets with a placeholder "TRADENAME" on the proposed container label.^a The Applicant submitted updated container label received on December 4, 2019 with the conditionally acceptable proprietary name Tazverik. However, our previous review recommendations have not been communicated to the applicant yet, and we identified additional areas in the December 4, 2019 container labels that may be improved.

2 CONCLUSION

The proposed container label received on December 4, 2019 is unacceptable from a medication error perspective. We provide our recommendations in Section 3 below.

3 RECOMMENDATIONS FOR EPIZYME INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Label

1. Remove "200 mg" so the established name reads "(tazemetostat) tablets". Also, present the entire established name in the same prominence.

^a Stewart J. Label and Labeling Review for Tazverik (NDA 211723). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 23. RCM No.: 2019-1113.

- a. Ensure the established name is at least half the size of the proprietary name to be in accordance with 21 CFR 201.10(g)(2).
2. To reduce clutter and improve readability on the principal display panel, relocate the “Each tablet contains...” equivalency statement to appear on the side panel.
3. Remove the statement (b) (4)
4. Revise the statement (b) (4) to read “Recommended dosage: See Prescribing Information.”
5. Remove “70038683” from the container label or relocate the number to avoid confusion with the lot number.
6. As currently presented, the format for the expiration date is not defined on the label. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
 - a. Ensure that there are no other numbers located in close proximity to the expiration date where it can be mistaken as the expiration date.
 - b. Ensure the lot number is clearly differentiated from the expiration date.
7. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.¹ The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling.

The draft guidance is available from:
<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>
8. Based on information contained in your submission, this product must be stored (b) (4) In the ‘Storage’

section of the side panel, add the statement [REDACTED] (b) (4)

[REDACTED]

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JANINE A STEWART
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CHI-MING TU
12/10/2019 12:09:45 PM

Clinical Inspection Summary

Date	November 7, 2019
From	Yang-min (Max) Ning, M.D., Ph.D. Aisha Johnson, M.D., M.P.H., M.B.A. Kassa Ayalew, M.D., M.P.H. OSI/DCCE/GCPAB
To	Leslie Doros, M.D. Ashley Ward, M.D. Kristin Jarrell, RPM OCE/OHOP/DOP2
NDA #	211723
Applicant	Epizyme Inc.
Drug	Tazemetostat
NME	Yes
Therapeutic Classification	Inhibitor of enhancer of Zeste Homolog 2 (EZH2)
Proposed Indication(s)	Treatment of adult patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery
Consultation Request Date	July 24, 2019
Summary Goal Date	November 19, 2019
Action Goal Date	January 25, 2020
PDUFA Date	January 25, 2020

I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

Clinical data from an open-label Phase 2 trial (Cohort 5 of EZH-202) were submitted to the Agency in support of this New Drug Application (NDA) for tazemetostat. Four clinical investigator sites (#8002, 8008, 8004, and 5001) and the contract research organization (CRO) that performed independent central review of tumor response data were selected for clinical inspections.

The inspections verified the Applicant's submitted clinical data with source data at the clinical investigator and CRO sites. Based on the results of these inspections, the data generated by these clinical investigator sites and the CRO, which were submitted by the Applicant, appear to be reliable and supportive of this application.

II. BACKGROUND

Tazemetostat is a small molecule inhibitor of enhancer of Zeste Homolog 2 (EZH2), a histone methyltransferase. To support the proposed indication in this NDA, the Applicant submitted clinical data from Cohort 5 of an ongoing, open-label Phase 2 trial (EZH-202) of tazemetostat in patients with integrase interactor 1 (INI1)-negative tumors or relapsed/refractory synovial sarcoma. Note that this Study EZH-202 has a total of seven cohorts and that the current application is primarily based on the interim analysis of Cohort 5.

Cohort 5 enrolled subjects with advanced epithelioid sarcoma (ES) with loss of INI1 as confirmed by immunohistochemistry or molecular confirmation of tumor bi-allelic INI1 loss or mutation when INI1 IHC was equivocal or unavailable. The primary endpoint for this cohort was the confirmed objective response rate (ORR) as assessed by the investigators. Independent central review (ICR) was performed to provide supportive evidence for the investigator-assessed results.

Subjects received tazemetostat 800 mg orally twice daily. Study treatment continued until confirmed disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study. Tumor response assessments were performed with CT/MRI scans every 8 weeks (\pm 3 days) for two years and thereafter subjects had an option to enroll in a rollover study. Scans were also submitted to the CRO for independent review according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1). The objective of the ICR was to provide supportive evidence for the Investigator-assessed ORR.

From 12/22/2015 through 9/17/2018 (data cutoff date for the analysis), the study enrolled 223 subjects, with 62 into Cohort 5. Forty of the 62 subjects were from 12 study sites in the U.S. and the rest of them were from 9 sites in Italy, Belgium, England, France, Canada, and Taiwan.

Four clinical investigator (CI) sites were selected for clinical inspections of the study, with a primary focus on Cohort 5. The CI Site 8002 had the highest number of subjects enrolled (13 of 62 subjects in Cohort 5) and had a high number of discordances between Investigator- and ICR-assessed best overall responses. Site 8008 had the highest number of responders per Investigator's assessment, with a site-specific response rate of 40% compared to the reported overall response rate of 15% in this cohort. Site 8004 also had a higher response rate (33%). Site 5001 had a relatively high number of subjects, with one responding subject who had the longest duration of response, which was ongoing at the time of the data cutoff for analysis. In addition, Site 5001 had a relatively lower incidence of reported adverse events (AEs), serious AEs, and deaths. With the noted discrepancies in tumor assessment results between the Investigators and ICR, the CRO ((b) (4)), which performed the ICR of scans, was also selected for clinical inspection.

III. RESULTS

1. Dr. Mrinal Gounder: Clinical Investigator (CI) Site # 8002

This CI site was inspected on September 10-13, 2019 as a data audit for the Study EZH-202 (Cohort 5). For the investigator, this was the first FDA inspection. The site enrolled 13 subjects in Cohort 5. All the subjects received at least one dose of study treatment. As of the data cutoff, 12 subjects were discontinued of study treatment secondary to disease progression, and one subject withdrew consent.

All the subjects' source records were reviewed during the inspection. These records included but were not limited to the enrollment logs, informed consent forms (ICFs), delegation logs, study protocol, Institutional Review Board (IRB) correspondence and approvals, scans and relevant RECIST assessments, laboratory results, adverse events (AEs), test article accountability records, concomitant medicines, monitoring logs, sponsor correspondence files, and protocol deviations. The inspection also reviewed the Investigator's responsibilities and relevant documentation processes, including the signed FDA 1572s, financial disclosures, data management and retention at the site.

The Applicant's submitted data listings for this site were compared with the source records and were found to be consistent. The inspection reported no objectionable observations in GCP compliance, with no Form FDA 483 issued to the investigator at the end of the inspection. There was no evidence of under-reporting of adverse events.

2. Dr. Victor Villalobos: Clinical Investigator (CI) Site # 8008

This CI Site 8008 was inspected on September 16-19, 2019 as a data audit for the study EZH-202 (Cohort 5). This was the initial FDA inspection of this clinical investigator. As of the data cutoff date, the site enrolled five subjects in Cohort 5. Of the five subjects, one (Subject (b) (6)) remained on study treatment, four were discontinued due to disease progression (Subjects (b) (6)) or unacceptable toxicity (Subject (b) (6)). At the time of the inspection, Subject (b) (6) continued receiving study treatment.

Source documents for all subjects in the cohort were reviewed and compared with the submitted data listings to the NDA for this site. The reviewed source documents involved the demographics of the subjects, inclusion and exclusion criteria, informed consent forms (ICF), exposure to the investigational product, scans and tumor response records, laboratory test results, adverse events, and concomitant medications. The inspection also examined documents related to the conduct of this study at the site, including the study protocol, IRB's approvals of the protocol, ICF and Subject

Calendar, signed Form FDA 1572s, signed Financial Disclosure Forms, Delegation of Authority log, Master Subject Log, investigational product accountability logs, and study monitoring records.

The inspection found no significant deficiencies in GCP compliance, with no Form FDA 483 issued at the end of the inspection. The submitted data listings were verifiable with the source documents.

Two inspectional findings were discussed at the close-out meeting. One finding was that for two instances, the investigational pharmacy did not dispense the investigational product based on the IVRS-generated lot numbers. The pharmacist informed the study coordinator of the second incident on the same day. However, this was not reported to the sponsor. The improper dispensations were identified in the sponsor's audition in August 2019 and reported to the IRB by the principle investigator. A preventive and corrective action (CAPA) has been implemented since then. The other finding was about one subject (Subject (b) (6)) who went to an emergency department (ED) for chest pain and thereafter left the ED against the medical recommendation to stay overnight for observation. Based on the medical record obtained from the ED and the follow-up study visit occurring 2 days after the ED visit, a sub-investigator (NP) concluded that the event was not an SAE and thus not reportable. The principal investigator acknowledged the finding and stated that he would take steps to correct.

(Reviewer's Comments: The dispensation of the incorrect lots of the investigational product was verified in the current inspection. The implemented CAPA is considered acceptable to prevent the same issue from reoccurring. Regarding the chest pain in Subject (b) (6) who left the ED against the medical advice for overnight observation, the event was reported. However, it should be considered serious and reported to the sponsor as an SAE per the protocol, in which the definition for a serious AE included "when in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious".)

3. Dr. Thierry Jahan: Clinical Investigator (CI) Site # 8004

This CI site was inspected between 9/24/2019 and 10/3/2019 as a data audit for the study EZH-202 (Cohort 5). For the investigator, this was the first FDA Inspection. The site enrolled a total of 9 subjects into the study, with 3 subjects ((b) (6)) in Cohort 5. As of the data cutoff date, all the subjects, including the 3 subjects in Cohort 5, were discontinued due to disease progression. Subject (b) (6) died from the study disease.

Source documents for all the enrolled study subjects were reviewed during the inspection, including the informed consent forms (ICFs), eligibility, cohort assignments, CT/MRI scans, tumor response reports, adverse events, protocol deviations/violations, discontinuations, concomitant medications, test article accountability and disposition, training records, and regulatory documents (e.g., the IRB's approvals, Delegation of Responsibility/Authority Log, signed Form FDA 1572s and Financial Disclosure

Forms).

The Applicant's submitted data listings for this site were verifiable with the source records, with no evidence of underreporting of adverse events. The inspection found no significant objectionable observations in the study conduct at this site. No Form FDA 483 was issued to the investigator.

There were several discussion items shared with the study team at the close-out meeting. These items mostly related to documentation and reporting practices at the site: 1) one sub-investigator was not listed in the delegation of duty log and did not sign his financial disclosure form; 2) inadequate documentation of study staff training for the study initiation visit; 3) some discrepancies in protocol deviations were noted between the data listings and source records; 4) for two subjects (Subjects (b) (6)) who received concomitant medicines, the stopping date or the start date was not documented or accurately documented on their eCRF. The principle investigator acknowledged the findings and stated his plans to address each of them accordingly and prevent from reoccurring in the future. Note that the Discussion Item 1 was addressed before the closeout meeting.

4. Dr. Silvia Stacchiotti: Clinical Investigator (CI) Site # 5001

This foreign CI site was inspected on October 21-24, 2019 as a data audit for the study EZH-202 (Cohort 5). This was the first FDA clinical inspection for the investigator. The inspection report is not currently available. Based on the preliminary summary provided by the inspector, the site enrolled 6 subjects into the cohort. As of the data cutoff date, two subjects ((b) (6)) remained on study treatment and four were discontinued due to disease progression. At the time of inspection, Subject (b) (6) remained on study treatment and Subject (b) (6) was discontinued due to disease progression.

The inspection reviewed all subjects' source documents, including medical history, informed consents, diaries, radiological reports, tumor assessment worksheets, laboratory tests, case report forms, etc. The inspection found that the reported efficacy and safety data were verifiable with the source documents. There was no evidence of underreporting of adverse events. Numerous protocol deviations at the site were found to have already reported to the sponsor.

No Form FDA 483 was issued to the investigator. At the closeout meeting, the importance of following the study protocol was discussed. Most of the reported deviations occurred at the beginning of the study. Thereafter, adequate corrective measures have been implemented at the site.

(Note: An amendment to this inspection summary will be introduced if the EIR for Dr. Stacchiotti's site contains considerable differences that affect the GCP assessment conclusion for this site.)

5. CRO: [REDACTED] (b) (4)

[REDACTED] (b) (4) was inspected on August 26-27, 2019 for its conduct of ICR and verification of the submitted data for Cohort 5 of the Study EZH-202. This was the first FDA inspection of this imaging CRO.

The current inspection reviewed relevant CRO's documents to this study, including the organizational charts, standard operating procedures, protocols, study reports, transfer of responsibilities, correspondence, training records, electronic records of subject scan results, training documentation and site qualification. The inspection focused on the [REDACTED] (b) (4) process for conducting IRC and examined the qualification and training of participating radiologists as well as the related quality control (e.g., de-identification of images and adjudication of review findings) in use of the [REDACTED] (b) (4) electronic systems [e.g., ClinTRAK, DICOM, and MintLesion) for central review and data reporting.

The reported best overall responses for all 62 subjects in Cohort 5 were examined against the [REDACTED] (b) (4) records and were found to be consistent with the data submitted to the NDA. For each of the reported nine responding subjects (Complete Response or Partial Response), select scans were examined for the [REDACTED] (b) (4) acquisition and retention. The majority of the examined scans were submitted within three weeks. Delayed scan submissions (>28-50 days) were uploaded upon completion of queries.

This inspection found no GCP compliance deficiencies, with no Form FDA 483 issued. Overall, the ICR for Cohort 5 of the study EZH-202 was adequately performed by the CRO.

PRIMARY REVIEW: { See appended electronic signature page }

Yang-min (Max) Ning, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Aisha Johnson, M.D., M.P.H., M.B.A.
Acting Team Lead
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

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Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

cc:

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Review Division /Cross Discipline Team Leader/A Ward
Review Division /Project Manager/K Jarrell
Review Division/Medical Officer/L Doros
OSI/Office Director/D Burrow
OSI/DCCE/ Division Director/N Khin
OSI/DCCE/Branch Chief/K Ayalew
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OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 4, 2019

To: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Ruth Mayrosh, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Emily Dvorsky, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): TAZVERIK (tazemetostat)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 211723

Applicant: Epizyme, Inc.

1 INTRODUCTION

On May 23, 2019, Epizyme, Inc. submitted for the Agency's review an original New Drug Application (NDA) 211723 for TAZVERIK (tazemetostat) tablets.

TAZVERIK (tazemetostat) is a New Molecular Entity (NME) with a proposed indication for the treatment of people with metastatic or locally advanced epithelioid sarcoma not eligible for curative surgery.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on July 21, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TAZVERIK (tazemetostat) tablets.

2 MATERIAL REVIEWED

- Draft TAZVERIK (tazemetostat) tablets MG received on May 23, 2019, and received by DMPP and OPDP on October 24, 2019.
- Draft TAZVERIK (tazemetostat) tablets Prescribing Information (PI) received on May 23, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 24, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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MORGAN A WALKER
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LASHAWN M GRIFFITHS
11/04/2019 08:54:39 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 1, 2019

To: Leslie Doros, M.D., Medical Officer
Division of Oncology Products 2 (DOP2)

Kristin Jarrell, PharmD, Regulatory Project Manager, (DOP2)

Stacy Shord, PharmD, Associate Director for Labeling, (DOP2)

From: Emily Dvorsky, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for TAZVERIK (tazemetostat) tablets, for oral use

NDA: 211723

In response to DOP2's consult request dated July 21, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for TAZVERIK (tazemetostat) tablets, for oral use.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DOP2 (Kristin Jarrell) on October 23, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 22, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or Emily.Dvorsky@fda.hhs.gov.

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EMILY M DVORSKY
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 23, 2019
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 211723
Product Name and Strength:	Tazverik (tazemetostat) Tablets, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Epizyme Inc.
FDA Received Date:	May 23, 2019, August 9, 2019, and August 22, 2019
OSE RCM #:	2019-1113
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1 REASON FOR REVIEW

This review responds to a request from DOP2 to review the proposed container label and prescribing information (PI) submitted for Tazverik (tazemetostat) tablets for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters*	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, and PI for Tazverik (tazemetostat) to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas in the PI, carton labeling and container labels that can be modified to improve the clarity of the information presented.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed PI and container label can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for Epizyme in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Replace "TRADENAME" with the conditionally acceptable name "Tazverik" wherever it appears.
2. Consider adding the number of tablets after the milligram dose in Section 2 of PI. For example, "... 800 mg (four 200 mg tablets)..." and "600 mg (three 200 mg tablets)".

4.2 RECOMMENDATIONS FOR EPIZYME INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Label

1. Replace "TRADENAME" with the conditionally acceptable name "Tazverik" wherever it appears.
2. To reduce clutter and improve readability on the principal display panel, relocate the "Each tablets contains..." equivalency statement to appear on the right side panel.
3. Remove the statement [REDACTED] (b) (4) or relocate it to below the strength statement "200 mg".
4. Revise the statement [REDACTED] (b) (4) to read "Recommended dosage: See Prescribing Information."
5. Consider removing "7003xxxx" from the container label or relocate to next to the "manufactured for" information to avoid confusion with the lot number.
6. Based on information contained in your submission, this product must be stored [REDACTED] (b) (4). In the 'Storage' section of the side panel, add the statement [REDACTED] (b) (4).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tazverik received on August 9, 2019 from Epizyme Inc..

Table 2. Relevant Product Information for Tazverik	
Initial Approval Date	N/A
Active Ingredient	tazemetostat
Indication	For the treatment of adult patients with metastatic or locally advanced epithelioid sarcoma (ES) who are not eligible for curative surgery.
Route of Administration	Oral
Dosage Form	Tablets
Strength	200 mg
Dose and Frequency	800 mg orally twice daily with or without food until disease progression or unacceptable toxicity. Dose reduction for adverse reactions: 1 st dose reduction is 600 mg twice daily, and 2 nd dose reduction is 400 mg twice daily. Discontinue if further dose reduction is required.
How Supplied	Bottles of 240 tablets
Storage	(b) (4) Do not store above 30 °C (86 °F).
Container Closure	215 mL white square HDPE bottle with a (b) (4) cap and 2 g desiccant.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Tazverik labels and labeling submitted by Epizyme Inc..

- Container label received on August 22, 2019
- Medication Guide (Image not shown) received on May 23, 2019
- Prescribing Information (Image not shown) received on August 9, 2019

G.2 Label and Labeling Images

Container Label



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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10/23/2019 10:36:15 AM

CHI-MING TU
10/23/2019 10:51:45 AM

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA
Submission Number	211723
Submission Date	5/23/2019
Date Consult Received	7/26/2019
Clinical Division	DOP2

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- [Previous QT-IRT reviews](#) under IND 124608 dated 04/27/2017 and 07/24/2017 in DARRTS;
- Proposed [label](#) (Submission 0010);
- Study E7438-G00-101 [clinical study report](#), [cardiac safety report](#), and [concentration-QTc report](#) (Submission 0001)

1 SUMMARY

No large QTc prolongation effect (i.e., >20 ms) of tazemetostat was observed in this QT assessment.

The effect of tazemetostat was evaluated in the dose escalation/dose expansion cohorts in the Phase 1 part of Study E7438-G000-101. The highest dose that was evaluated was 1600 mg BID, which covers the therapeutic dose 800 mg BID. The data was analyzed using exposure-response analysis as the primary analysis, which did not suggest that tazemetostat is associated with large mean increases in the QTc interval (refer to section 4.5) – see Table 1 for overall results. The findings of this analysis are further supported by the central tendency analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Concentration	Δ (ms)	90% CI (ms)
QTc	Tazemetostat 800 mg	1553.9	6.1	(3.8, 8.5)
QTc	Tazemetostat 1600 mg	3146.9	9.3	(6.2, 12.5)

The highest exposure scenario has not be determined since the drug-drug interaction and hepatic impairment studies are pending. The high clinical exposure scenario is expected to occur with CYP3A4 inhibitor coadministration or in patients with hepatic impairment. A postmarketing-requirement for both evaluations will be issued upon approval.

A positive concentration-QTc relationship cannot be ruled out in this clinical assessment. The sponsor's in vitro hERG assay is insufficient to calculate an IC50 value.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable

2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0010 from the QT-IRT. Our changes are highlighted ([addition](#), [deletion](#)). This is a suggestion only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of orally administered TRADENAME, at doses ranging from 100 mg to 1600 mg twice daily (b) (4)

(b) (4) Tazemetostat and its (b) (4) metabolite EPZ-6930 did not cause [large mean increase \(i.e. >20 ms\) on the QTc interval at the 800 mg BID dose](#) (b) (4)

[The largest mean increase \(upper bound of 90% confidence interval\) in QTc were 6.1 ms \(8.5 ms\) and 9.3 ms \(12.5 ms\) at the 800 mg BID and 1600 mg BID dose levels, respectively.](#)

- *The study design does not support an exclusion of small effect (i.e. 10 ms). We propose to specify the scope of the analysis (i.e. large effect) in the label.*
- *Drug exposure in the presence of drug-drug interaction and organ impairment has not been determined. The term (b) (4) can be misleading. In addition, a positive concentration-QTc relationship cannot be ruled out in this clinical assessment. We propose to report the numerical estimates at the specific dose levels.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Previously the QT-IRT reviewed the concentration-QTc analysis plan based on study E7438-G000-101 (IND 124608, dated 04/27/2017 and 07/24/2017 in DARRTS). It was concluded that the study may have adequate information to exclude large mean effect. The sponsor was advised to provide by-timepoint descriptive statistics.

Study E7438-G000-101 is an open-label, multicenter, Phase 1/2 study of tazemetostat as a single agent in subjects with advanced solid tumors or with B-cell lymphomas. A total of 64 patients were included in the Safety Population. Data from 38 subjects who participated in the Phase 1 Dose Escalation and Dose Expansion part were included in the present QT assessment. Five dose levels were explored: 100 mg BID, 200 mg BID, 400 mg BID and 1600 mg BID. PK/ECG samples were collected at predose, 0.5, 1, 2, 4, 6, 8, and 12 hr postdose on Cycle 1, Day 1 and 15. The sponsor used QTcI as the primary endpoint and QTcF as the secondary endpoint.

Mean (\pm s.e.) inhibition of hERG potassium current was 15.1 (1.4%) at 10 μ mol/L tazemetostat in HEK293 cells. Tazemetostat had no effects on cardiovascular parameters in conscious, telemetered cynomolgus monkeys at single oral doses up to 1000 mg/kg,

and had no notable effects on ECG parameters in monkeys treated with repeat doses of tazemetostat for up to 13 weeks.

Reviewer's comments: Assuming a fraction unbound of 12%, free C_{max} at the 800 mg BID dose level is approximately 300 nM. The ratio between in vitro hERG IC₅₀ (>10 μM) and free C_{max} should be >30-fold for the proposed therapeutic dose.

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

The primary analysis is concentration-QTc analysis. The sponsor used parametric statistics in central tendency analysis. Given the small sample size, FDA reviewer used non-parametric statistics in the central tendency analysis. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT bias assessment

None.

3.2.2 Categorical Analysis

The results of the reviewer's analysis are similar to the sponsor's results for QTcF and ΔQTcF. None of the subjects had absolute QTcF > 500 ms. One subject's change from baseline was above 60 ms in tazemetostat 800 mg group.

For HR, PR and QRS, sponsor defined outliers if HR, PR and QRS are greater than 100 bpm, 200 ms and 100 ms respectively and at least 25% increase from baseline.

According to their definition, there were no outliers. FDA reviewer used standard categorical analysis intervals and there were few subjects in extreme categories in HR, PR and QRS. Please see section 4.4 for additional details.

3.2.3 Cardiac Safety

There were no cardiac deaths or SAEs reported in Phase 1 portion of the study (N=64).

One subject (ID (b) (6)) in the 800 mg BID dose group reported an AE of QT prolongation (Grade 1). This subject was in the Drug Drug Interaction cohort of the Phase 1 study and was not included in the IRT analysis.

3.2.4 Exposure-Response Analysis

There were 517 available ECG assessments available from the Phase 1 Dose Escalation and Dose Expansion parts of Study E7438-G000-101. In the primary analysis, the sponsor excluded subject (b) (6) because the subject had hypercalcemia at baseline and had unexpectedly higher QTc values on Cycle 1 Day 15 than the rest of the patient population despite of regular drug exposure. The sponsor used QTcI as the primary endpoint. The final model included tazemetostat concentration and nominal time points (0, 2, 4, and 12 hr) as the fixed effects and included between-subject variability on the intercept. The analysis suggested a statistically positive slope (0.00127 mg/(ng/mL)).

The model-predicted upper bound of the 90% CI of ΔQTcI did not exceed 10 ms over the observed concentration ranges for tazemetostat. A similar analysis was conducted using the major metabolite, EPZ-6930, as the exposure metrics. The concentration- QTc slope was not statistically significant, and the 90% CI of the predicted ΔQTcI include 0. Inclusion of the outlier substantially increased the concentration- QTc slope for both tazemetostat and EPZ-6930, and resulted in a higher SD for the intercept and residual error.

When QTcF was used as the dependent variable, the mean and upper bound of the 90% CI of ΔQTcF were predicted not to exceed 20 ms over the observed concentration ranges for tazemetostat and EPZ-6930.

After review of individual PK/ECG data, the reviewer agrees with the exclusion of subject (b) (6) from the primary analysis. The reviewer does not agree with including nominal time points as a fixed effect covariate in the model when a proper control arm is absent. Similar to the sponsor's results for QTcF , the reviewer's analysis suggests a statistically significant, positive concentration- QTc slope. Please see section 4.5 for additional details.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcI for the primary analysis. The reviewers used QTcF as the primary endpoint as no significant increases or decreases in heart rate (i.e. mean < 10 bpm) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

None.

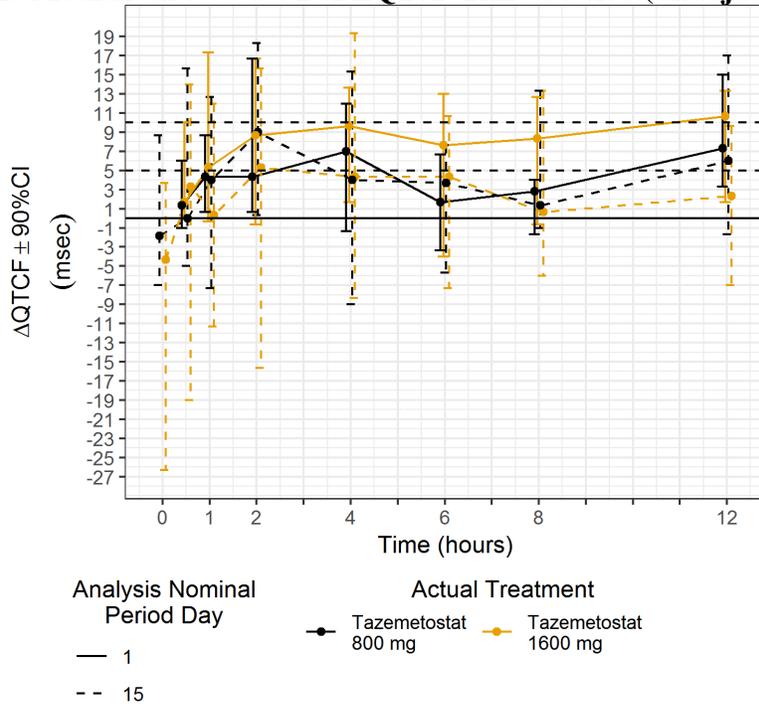
4.3 CENTRAL TENDENCY ANALYSIS

The statistical reviewer used non-parametric method for the exploratory analysis for QTcF , HR, PR and QRS.

4.3.1 QTc

The following figure displays the time profile of ΔQTcF for different treatment groups.

Figure 1: Median and 90% CI of Δ QTcF Time Course (unadjusted CIs).



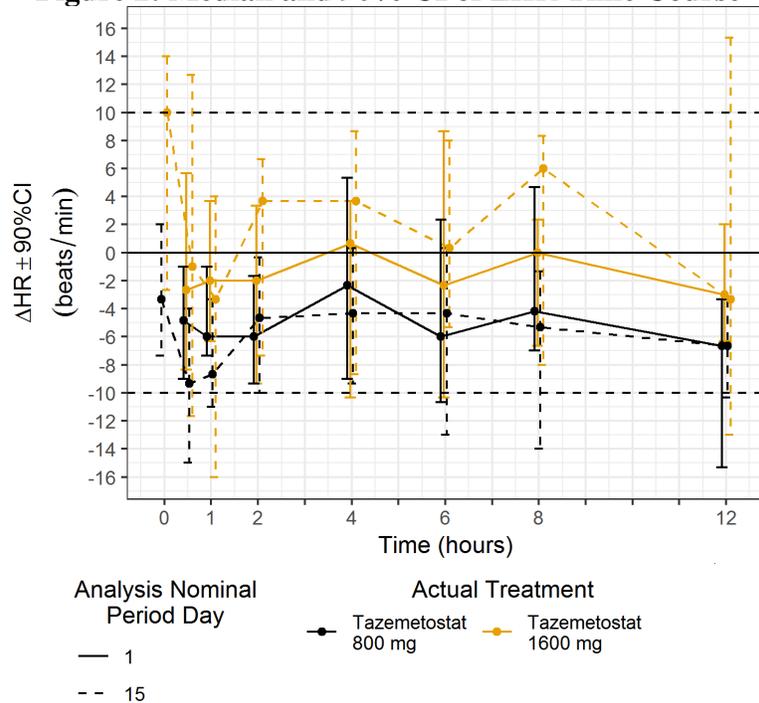
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

The same statistical analysis was performed based on HR (Figure 2).

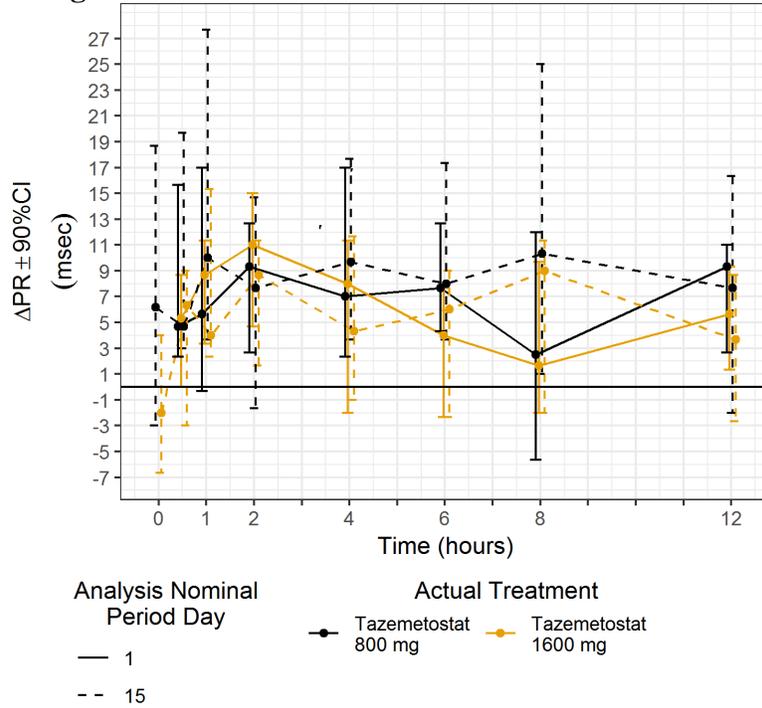
Figure 2: Median and 90% CI of Δ HR Time Course



4.3.3 PR

The same statistical analysis was performed based on PR interval (Figure 3).

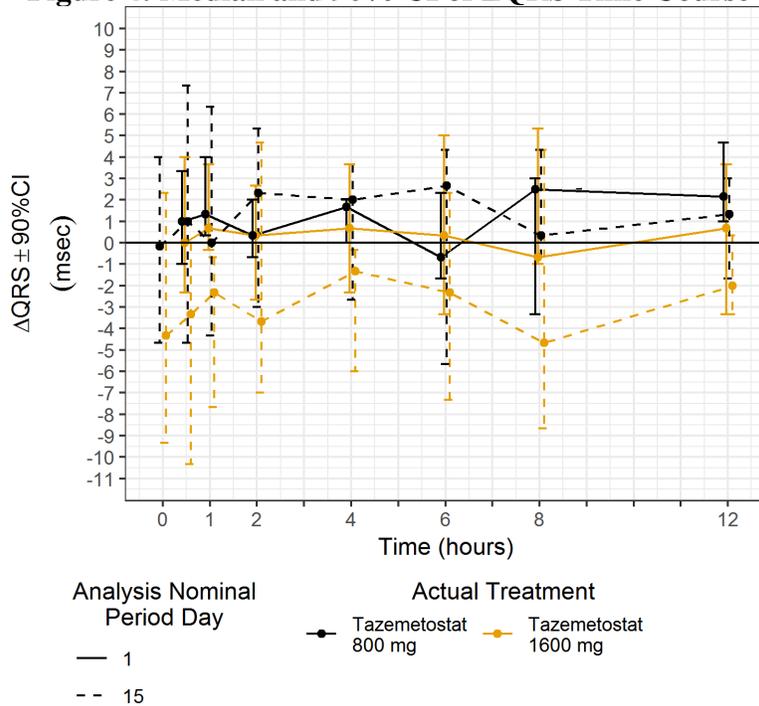
Figure 3: Median and 90% CI of Δ PR Time Course



4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 4).

Figure 4: Median and 90% CI of Δ QRS Time Course



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

Table 2 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480ms and 500 ms. No subject's QTcF was above 500 ms.

Table 2: Categorical Analysis for QTcF

Actual Treatment	Total (N)		Value ≤ 450 msec		450 msec < Value ≤ 480 msec		480 msec < Value ≤ 500 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Tazemetostat 100 - 400 mg	12	176	10 (83.3%)	174 (98.9%)	2 (16.7%)	2 (1.1%)	0 (0%)	0 (0%)
Tazemetostat 800 mg	14	197	11 (78.6%)	168 (85.3%)	2 (14.3%)	28 (14.2%)	1 (7.1%)	1 (0.5%)
Tazemetostat 1600 mg	11	165	10 (90.9%)	164 (99.4%)	1 (9.1%)	1 (0.6%)	0 (0%)	0 (0%)

Table 3 lists the categorical analysis results for Δ QTcF. One subject's change from baseline was above 60 ms in tazemetostat 800 mg group. Subject E7438-G000-101-^{(b) (6)} had a maximum of 471 ms post-baseline and 388 ms baseline values for QTcF, leading to 78 ms in Δ QTcF.

Table 3: Categorical Analysis of Δ QTcF

Actual Treatment	Total (N)		Value ≤ 30 msec		30 msec < Value ≤ 60 msec		Value > 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Tazemetostat 100 - 400 mg	12	176	10 (83.3%)	173 (98.3%)	2 (16.7%)	3 (1.7%)	0 (0%)	0 (0%)
Tazemetostat 800 mg	14	197	10 (71.4%)	182 (92.4%)	3 (21.4%)	8 (4.1%)	1 (7.1%)	7 (3.6%)
Tazemetostat 1600 mg	11	165	10 (90.9%)	162 (98.2%)	1 (9.1%)	3 (1.8%)	0 (0%)	0 (0%)

4.4.2 PR

The outlier analysis results for PR are presented in Table 4. There are two subjects who experienced PR interval greater than 220 ms in tazemetostat 100-400 mg and tazemetostat 1600 mg groups. The increase from baseline for both subjects was less than 25%.

Table 4: Categorical Analysis for PR

Actual Treatment	Total (N)		Value ≤ 220 msec		Value > 220 msec & < 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Tazemetostat 100 - 400 mg	12	176	11 (91.7%)	174 (98.9%)	1 (8.3%)	2 (1.1%)
Tazemetostat 800 mg	14	197	14 (100.0%)	197 (100.0%)	0 (0%)	0 (0%)
Tazemetostat 1600 mg	11	165	10 (90.9%)	150 (90.9%)	1 (9.1%)	15 (9.1%)

4.4.3 QRS

The outlier analysis results for QRS are presented in Table 5. There are two subjects who experienced QRS interval greater than 110 ms in tazemetostat 100-400 mg and tazemetostat 800 mg groups. The increase from baseline for both subjects was less than 25%.

Table 5: Categorical Analysis for QRS

Actual Treatment	Total (N)		Value <= 120 msec		Value > 120 msec & < 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Tazemetostat 100 - 400 mg	12	176	11 (91.7%)	162 (92.0%)	1 (8.3%)	14 (8.0%)
Tazemetostat 800 mg	14	197	13 (92.9%)	184 (93.4%)	1 (7.1%)	13 (6.6%)
Tazemetostat 1600 mg	11	165	11 (100.0%)	165 (100.0%)	0 (0%)	0 (0%)

4.4.4 HR

The outlier analysis results for HR are presented in Table 6. There are 6 subjects who experienced HR greater than 100 bpm in in tazemetostat 100-400 mg, tazemetostat 800 mg and tazemetostat 1600 mg groups respectively. Among 6 subjects, 2 subjects had post-baseline HR value greater than 25% compare to the baseline HR.

Table 6: Categorical Analysis for HR

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Tazemetostat 100 - 400 mg	12	176	11 (91.7%)	175 (99.4%)	1 (8.3%)	1 (0.6%)
Tazemetostat 800 mg	14	197	12 (85.7%)	189 (95.9%)	2 (14.3%)	8 (4.1%)
Tazemetostat 1600 mg	11	165	8 (72.7%)	144 (87.3%)	3 (27.3%)	21 (12.7%)

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between drug concentration and Δ QTcF. The reviewer's primary analysis does not include data from subject (b) (6)

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and Δ QTcF and 3) presence of non-linear relationship.

An evaluation of the time-course of drug concentration and changes in Δ HR and Δ QTcF is shown in Figure 2 and Figure 5, which shows an absence of significant changes in HR and do not appear to show significant hysteresis. Figure 6 shows the relationship between drug concentration and Δ QTcF and supports the use of a linear model. Tazemetostat and EPZ-6930 (major metabolite) concentration increase with dose. Tazemetostat concentration is higher after a single dose than after multiple doses which is likely due to autoinduction, and there is accumulation of the EPZ-6930 exposure.

Figure 5: Time course of tazemetostat concentration (top), EPZ-6930 concentration (middle), and QTcF (bottom)

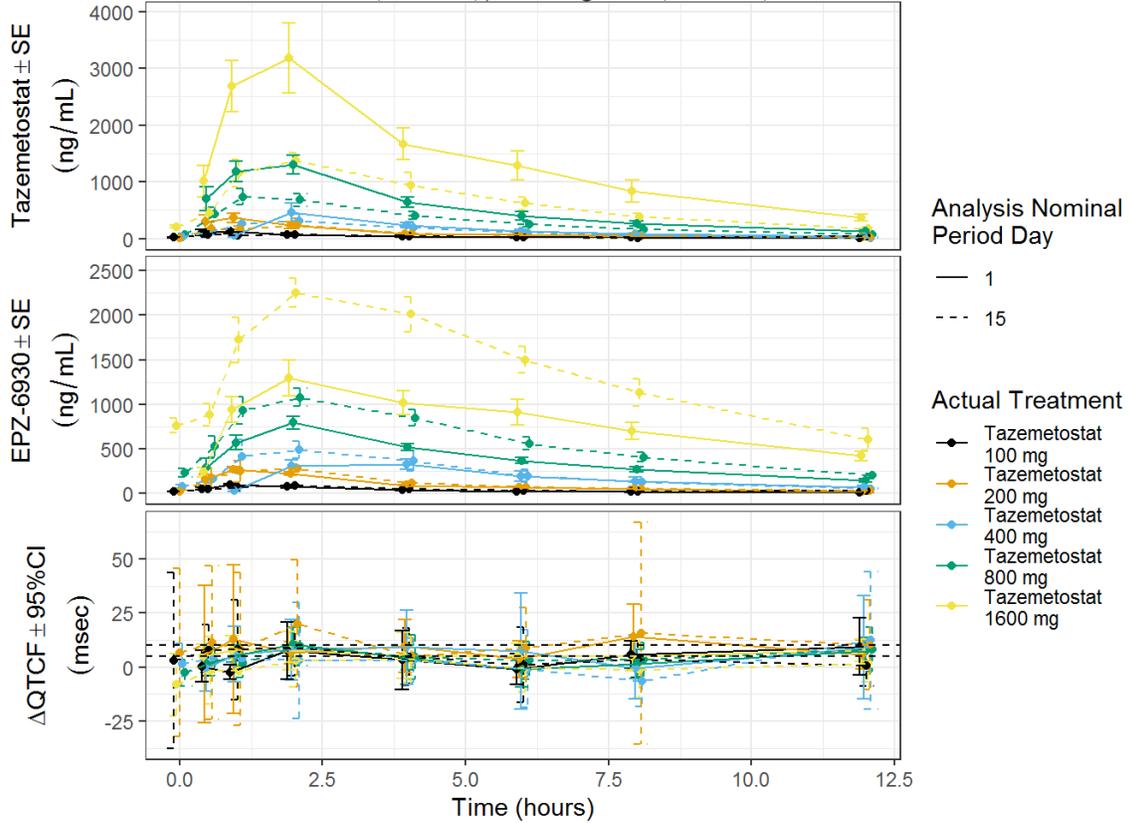
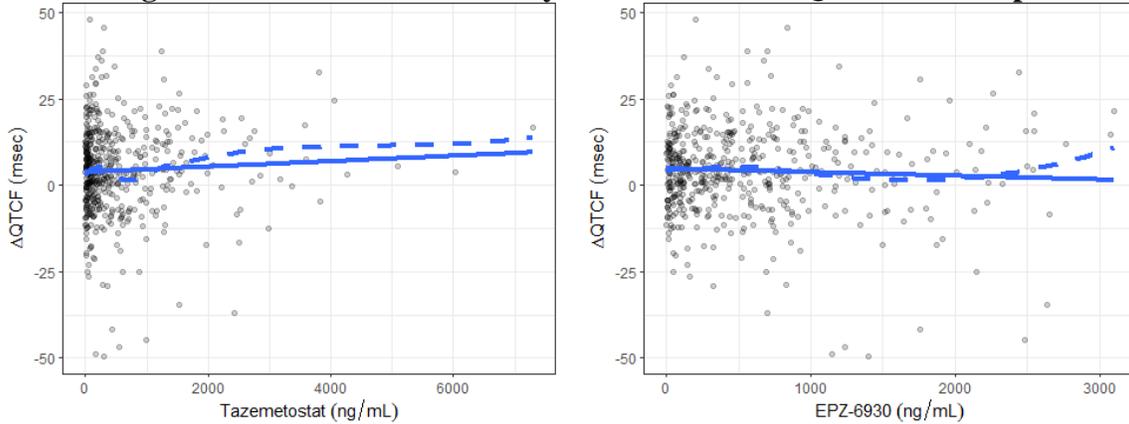
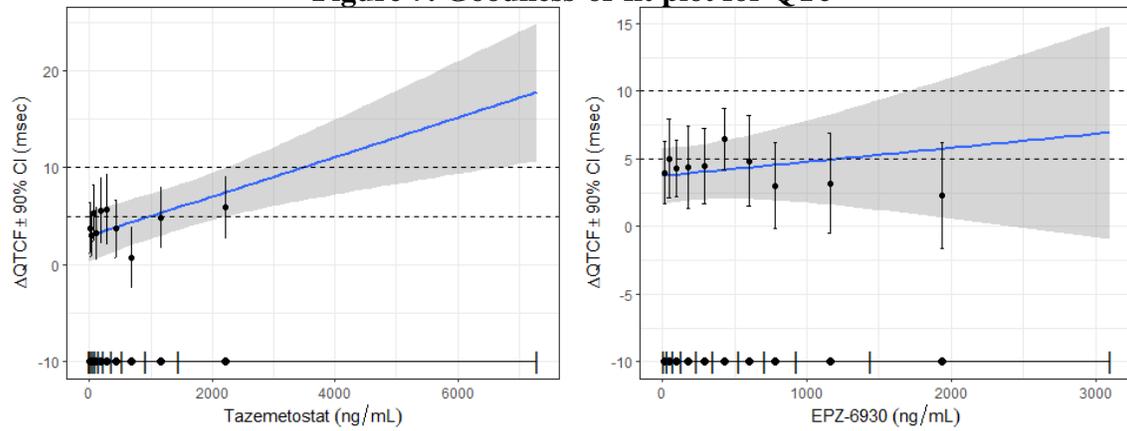


Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model with intercept, tazemetostat or EPZ-6930 concentration, and baseline QTcF was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the tazemetostat concentration-QTc model are provide in Table 1: The Point Estimates and the 90% CIs (FDA Analysis). The analysis suggested a statistically significant positive concentration-QTc relationship with tazemetostat but not EPZ-6930.

Figure 7: Goodness-of-fit plot for QTc



In the sensitivity analysis including subject (b) (6), the concentration-QTc slope remains statistically significant for tazemetostat and not significant for EPZ-6930. The predicted Δ QTcF at the geometric mean C_{max} at the 800 mg BID dose is 7.5 ms (90% CI: 4.4 to 10.7 ms).

4.5.1 Assay sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.3. No additional safety analyses were conducted.

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/s/

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Yuan Xu is the primary clinical pharmacology reviewer.

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