

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213400Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

IND 124025

MEETING MINUTES

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

Dear Dr. Jiang:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tazemetostat (EPZ-6438).

We also refer to the meeting between representatives of your firm and the FDA on October 24, 2019. The purpose of the meeting was to discuss aspects of the planned tazemetostat NDA submission, including content for clinical efficacy and safety.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Thomas Iype, Regulatory Health Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: October 24, 2019; 3:00 pm – 4:00 pm (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 21, Conference Room: 1539
Silver Spring, Maryland 20903

Sponsor Name: Epizyme, Inc.
Application Number: IND 124025
Product Name: Tazemetostat
Indication: Treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least 2 prior systemic therapies

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Thomas Iype, PharmD, RPh

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products

Albert Deisseroth, MD, PhD, Associate Division Director

Nicole Gormley, MD, *Clinical Team Leader*

R. Angelo de Claro, MD, *Clinical Team Leader*

Margret Merino, MD, *Clinical Reviewer*

Office of Biostatistics/Division of Biometrics V

Jingjing Ye, PhD, *Biometrics Team Leader*

Haiyan Chen, PhD, *Biometrics Reviewer*

Office of New Drug Products/Division of New Drug Products I

Sherita McLamore, *Regulatory Review Chemist*

Center for Devices and Radiological Health/Office In Vitro Diagnostics and Radiological Health/Division of Molecular Genetics and Pathology

Fengmin Li, PhD, *Reviewer*

Anand Pathak, MD, *Reviewer*

SPONSOR ATTENDEES

Deyaa Adib, MD, *Interim NHL Medical Director, Clinical Research*

Shefali Agarwal, MBBS, MPH, MIS, *Chief Medical Officer*

Robert Bazemore, *President and Chief Executive Officer*

Mark De Rosch, PhD, FRAPS, *Chief Regulatory Officer*
James Huebner, MS, MS, *Director, Program Management*
Huiping Jiang, PhD, *Vice President, Regulatory Affairs*
Neil Michaud, PhD, *Director, Translational Medicine*

(b) (4)

Vikram Kansra, PhD, *Clinical Pharmacology and Pharmacometrics*
John Leonard, MD, *Professor at the New York-Presbyterian Hospital and Weill Cornell Center for Lymphoma and Myeloma*
John Pagel, MD, PhD, *Chief, Hematologic Malignancies and Director of Stem Cell Transplantation, Swedish Cancer Institute*

1.0 BACKGROUND

Tazemetostat is a proposed inhibitor of histone methyltransferase (HMT) enhancer of zeste homolog 2 (EZH2) currently in development by Epizyme, Inc. for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least two prior systemic therapies. Fast track designation was granted on April 19, 2017, for the treatment of relapsed or refractory follicular lymphoma, and orphan drug designation granted on November 14, 2017, for the treatment of follicular lymphoma.

The Sponsor is currently planning on submitting a New Drug Application (NDA) by first quarter 2020 to support registration of tazemetostat for the treatment of adult patients with R/R FL who have received at least 2 prior systemic therapies via the 505(b)(1) pathway. On August 20, 2019, the Sponsor requested a Pre-NDA meeting with the Agency to discuss the components of their planned NDA submission, including content for clinical efficacy and safety.

2. DISCUSSION

2.1. Clinical Efficacy and Safety: Adequacy of Clinical Data Package to Support the Planned NDA

Question 1a: *Given the unmet medical need in the treatment of 3L+ FL and the totality of evidence provided to support a favorable benefit-risk assessment of tazemetostat in the studied population, does the Agency agree that the proposed clinical data package is adequate to support an original NDA submission for accelerated approval for the treatment of adult patients with R/R FL who have received at least 2 prior systemic therapies?*

FDA Response to Question 1a: Based on the topline efficacy and safety data provided, the contents of the proposed application appear acceptable to support an

application submission planned for December 2019. Ultimately, the adequacy of the data to support approval will be a review issue.

The Agency recommends that the Sponsor provide detailed information on the reason for censoring for duration of response in the datasets to be submitted.

Discussion: No discussion occurred.

Question 1b: Based on data from Study E7438-G000-101 demonstrating a clinically meaningful response in both the EZH2 WT and EZH2 MT populations, and the high unmet medical need in the proposed indication, Epizyme believes (b) (4)
(b) (4) Does the Agency agree?

FDA Response to Question 1b: No, (b) (4)
(b) (4)

Discussion: Both CDER and CDRH concur with the Sponsor's submission plans for the NDA and PMA as noted in slide 4.

Question 2 (Planned Timing of Data Cut for Safety Database): Epizyme would like to gain agreement on the following proposed timing of safety data cut for the planned NDA in FL:

- a) Epizyme proposes to use safety data cut of 24 May 2019 for the planned FL NDA. Does the Agency agree that the proposed safety data cutoff date is acceptable?
- b) Epizyme proposes that a cutoff of 01 Jan 2020 be used for the planned 4-month safety update. Does the Agency agree that the proposed data cutoff date for the 4-month safety update is acceptable?

FDA Response to Question 2:

- a) Based on a planned NDA submission in December 2019, the proposed safety data cutoff of May 24, 2019, is acceptable.
- b) Based on a planned NDA submission in December 2019, the proposed 120-day safety update cutoff of January 1, 2020, is acceptable.

Discussion: No discussion occurred.

Question 3 (EZH2 Copy Number Gain Data): The findings from analysis of the various clinical outcome parameters, including ORR, decrease in tumor burden, time

on treatment, DOR, PFS, and OS, for R/R FL subjects whose EZH2 WT copy number status was determined indicated that there were no statistically significant correlations to suggest EZH2 WT CNG explains sensitivity to tazemetostat treatment. Based on the current analysis on EZH2 copy number versus multiple clinical activity measures (ORR, OS, PFS, DOR), Epizyme believes that EZH2 CNG does not predict clinical responses to tazemetostat. Does the Agency agree?

FDA Response to Question 3: The data provided is inconclusive in demonstrating that EZH2 CNG does not predict clinical responses to tazemetostat nor is it conclusive that EZH2 CNG is not contributing a prognostic benefit to the observed efficacy. The reasons are:

- You are missing a large number of samples (~44%) for which there is no data.
- You used WES to assess EZH2 CNG but did not validate WES for EZH2 CNG specifically, and therefore we cannot conclude that the WES is appropriate tool for detecting EZH2 CNG.
- You did not provide EZH2 specific validation for aCGH and an appropriate explanation for the complete failure.

Discussion: CDRH will provide comments after the meeting regarding the proposal to not include aCGH in study EZH-302. The Sponsor plans to assess EZH2 WT CNG using WES platform and providing qPCR validation in the NDA submission for cohort 5 of study E7438-G000-101.

Post Meeting Comments: CDRH has not accepted qPCR as an orthogonal method for accuracy. We recommend that you use fluorescence in situ hybridization (FISH) as the comparator for accuracy. You should establish a cutoff based on the the upper reference of normal (upper threshold based on the background signal in specimens without CNG). CDRH will review the validity of the NGS method for its analytical sensitivity (limit of detection), precision at the LoD, and accuracy (Gain/no gain status). Use of FISH as the comparator will enable confirmation of the LoD and CNG status.

2.2. Regulatory/Clinical

Question 4 (REMS): Epizyme believes that there are no additional risk management strategies needed beyond recommended labeling to sufficiently address safety concerns for the proposed treatment with tazemetostat and that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary to ensure that the benefits of tazemetostat administration outweigh the risks to FL patients. Does the Agency agree?

FDA Response to Question 4: This will be a review issue.

Discussion: No discussion occurred.

2.3. Administrative

Question 5 (Application Orientation Meeting): *Epizyme proposes to have an application orientation meeting with the Agency within 45 days of the NDA submission for the purpose of orienting the review team to the content and format of the application. Does the Agency agree that Epizyme should plan for such a meeting?*

FDA Response to Question 5: Yes, you should plan for an application orientation meeting that will provide a high-level overview of the data included in the application. The AOM should focus on the clinical modules. Provide slides to the Agency one week prior to the AOM for review and feedback.

Additional Clinical Pharmacology Comments:

Refer to the Written Responses conveyed on January 14, 2019, under IND 124608, which reflect the Agency's expectation of clinical pharmacology evaluations to support the NDA submission. Furthermore, it is the Agency's expectation that the NDA submission should be complete at the time of original NDA submission. The adequacy of your clinical pharmacology package to support an NDA submission will be determined at the time of filing. For clinical pharmacology studies that are not completed prior to NDA submission, adequate information on when, how, and why these studies are not completed, should be included in your submission package. The status of any ongoing clinical pharmacology studies should also be provided.

Discussion: No discussion occurred.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Agency reached agreement with the Sponsor on the definition and submission plan of a complete application.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components. However, we consider the complete EZH2 WT CNG validation package to be minor and expected to be submitted with the 120-day safety update.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF

and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.¹

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD & C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants² to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PerC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing

¹ <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

² See the guidance for industry "Formal Meetings Between the FDA and Sponsors or Applicants."

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

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Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA**,

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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ANDA, BLA, Master File (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.⁶

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification for *Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁷

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

⁶ <http://www.fda.gov/ectd>

⁷ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁸

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs,

⁸ <https://www.fda.gov/media/85061/download>
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including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR⁹: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹⁰

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues currently requiring further discussion concerning the submission of your application.

5.0 ACTION ITEMS

There are no action items.

6.0 ATTACHMENTS AND HANDOUTS

We make reference to your email correspondence on October 23, 2019, that contained a presentation titled "*Tazemetostat In Follicular Lymphoma*".

14 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

⁹ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹⁰ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

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/

ROMEO A DE CLARO
10/28/2019 07:12:51 PM

IND 124025

MEETING MINUTES

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

Dear Dr. Jiang:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tazemetostat.

We also refer to the meeting between representatives of your firm and the FDA on July 15, 2019. The purpose of the meeting was to further discuss the clinical design of the proposed confirmatory Phase 3 study (EZH-302) in patients with relapsed or refractory follicular lymphoma previously treated with an anti-CD20 regimen. In addition, Epizyme, Inc. requests to discuss the format and content of an application that is to be submitted under an accelerated pathway for patients with relapsed or refractory follicular lymphoma, who have received at least two prior systemic therapies.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Thomas Iype, Regulatory Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2
Meeting Date and Time: July 15, 2019; 3:00 pm – 4:00 pm (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Sponsor: Epizyme, Inc.
Application Number: IND 124025
Product Name: Tazemetostat
Indication: Tazemetostat is indicated for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least 2 prior systemic therapies.

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Thomas Iype, PharmD, RPh

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products

Albert Deisseroth, MD, PhD, *Supervisory Associate Division Director*

R. Angelo de Claro, MD, *Clinical Team Leader*

Margret Merino, MD, *Clinical Reviewer*

OHOP/Division of Hematology, Oncology and Toxicology

Shwu-Luan Lee, PhD, *Pharmacologist/Toxicologist*

Office of Biometrics/Division of Biometrics V

Jingjing Ye, PhD, *Biometrics Team Leader*

Haiyan Chen, PhD, *Biometrics Reviewer*

Office of Clinical Pharmacology/Division of Clinical Pharmacology V

Guoxiang Shen, PhD, *Clinical Pharmacology Team Leader*

Lili Pan, PhD, *Clinical Pharmacology Reviewer*

Office of New Drug Products/Division of New Drug Products I

Xing Wang, PhD, *Chemist*

Office of Devices and Radiological Health/Office of In Vitro Diagnostics and Radiological Health/Division of Molecular Genetics and Pathology

Donna Roscoe, PhD, *Branch Chief*

Fengmin Li, PhD, *Reviewer*

SPONSOR ATTENDEES

Robert Bazemore, PhD, *President and CEO*

Deyaa Adib, MD, *Interim NHL Medical Director, Clinical Research*

Shefali Agarwal, MBBS, MPH, MS, *Chief Medical Officer*

Huiping Jiang, PhD, *Vice President, Regulatory Affairs*

Pamela Strode, MS, *Senior Vice President, Regulatory Affairs and Quality Assurance*

Jie (Jay) Yang, PhD, *Vice President, Biostatistics*

(b) (6)

John Pagel, MD, PhD, *Chief, Hematologic Malignancies and Director of Stem Cell Transplantation, Swedish Cancer Institute*

(b) (6)

1.0 BACKGROUND

On December 19, 2018, an End-of-Phase 2 meeting between representatives from FDA and the Sponsor to discuss the efficacy data from the follicular lymphoma cohorts of a Phase 2 study (E7438-G000-101) to support an accelerated approval in adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies. The FDA recommended that the Sponsor conduct more than one randomized trial to confirm the clinical benefit of tazemetostat. This is a follow-up meeting to discuss the planned confirmatory Phase 3 study EZH-302 in patients who have received at least 1 prior systemic therapy.

Preliminary comments were sent to the sponsor on July 5, 2019. The Agency received Sponsor's responses on July 16, 2019, which included a revised trial design. Based on the Agency's preliminary comments, the sponsor requested further discussion to question 1a.

2.0 DISCUSSION

Question 1a: *Does the Agency agree that the proposed*
is acceptable to serve as the proposed

(b) (4)

(b) (4)

FDA Response to Question 1a:

No,

(b) (4)

Overall Development Strategy

For the proposed initial application submission for a FL indication, we recommend concurrent submission of a PMA with CDRH for EZH2 testing. This recommendation is based on differences in ORR between the EZH2 WT and MT

populations, and the safety signal of secondary malignancies including myelodysplastic syndrome and acute leukemia.

At the minimum, you should have a device available to identify single nucleotide variants for EZH2. You should also assess any differences in efficacy based on EZH2 copy number gain (CNG) and develop a test if differences in efficacy are noted.

For a single randomized trial as a confirmatory trial, the trial should be adequately designed, adequately conducted, internally consistent, and provide clinically meaningful and statistically persuasive efficacy findings with an acceptable risk-benefit profile. Given the issues noted with the design of EZH-302 and uncertainty whether adding tazemetostat to lenalidomide and rituximab would be successful, we recommend that you conduct two adequate and well-controlled trials to support regular approval in follicular lymphoma.

Primary Endpoint

Given the uncertainty in device performance and the treatment benefit in overall and biomarker directed population, we recommend you power your study based on primary endpoint of PFS in EZH2 mutation subpopulation rather than overall population. Overall population can be tested after the mutation subgroup. If there is any adaptation planned, provide detailed information including but not limited to the simulation scenarios, assumptions made in the simulation in terms of overall population and mutation subgroups, statistical analysis method with a plan for alpha adjustment for both interim and final analyses, algorithm of sample size adaptations based on interim result, methods on how to combine overall and biomarker-directed subgroups at interim or final analysis in testing for efficacy, suitable justification and/or literature support for the assumptions, and methods for handling missing data, simulation results and any programming codes for simulation in your complete protocol and statistical analysis plan. In the case the adaptation is based on unblinding of the data in interim, procedure and measures should be put in place to ensure trial conduct and integrity throughout the trial after the interim analysis.

Study Design

There are not enough details in your protocol synopsis for justification of your sample size and adaptive designs. Please address the following:

- a. In your stage 2 and 3 of the trial, even without any adaptive enrichment, your sample size may be underpowered because median PFS for lenalidomide + rituximab in AUGMENT is observed to be 39.4 months rather than your assumed 25 months. Please refer to FDA USPI on lenalidomide.
- b. For adaptive enrichment design to enrich a biomarker directed population, the diagnostics device or test would need to have adequate performance characteristics.

- c. Should you proceed with the adaptive enrichment design for stage 2 and 3, you will need to provide details to show control of type-I error. Given that the primary endpoint is time-to-event PFS with potential different censoring patterns for overall and mutation subgroups, it is unclear what assumptions you made in your sample size calculation, how the population is combined to test for efficacy at interim and final analysis.

Secondary Endpoints

It is unclear whether and how you will test the key secondary endpoints in case the primary endpoint tested positive at the interim analysis. In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints, subgroups, or further analyses of the primary endpoint cannot result in (either singly or in combination) an efficacy claim. In the event that there is a statistically significant result for the primary analysis of the primary endpoint those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label. Please include in a future submission, any secondary endpoints for which claims may be included in the labeling and how adjustments will be made for multiplicity to guarantee a study-wise one-sided 0.025 type I error rate.

We found inconsistent statement regarding the key secondary endpoints. Under Section Secondary Objectives of the Study protocol synopsis, you stated that “The Key secondary objective is to evaluate and compare the ORR”. However, under Section Analysis of Secondary Efficacy Endpoints, you stated that “The key efficacy endpoints of OS and PFS.....” Please clarify.

Biomarker Testing

- a. We note that you previously proposed to employ array comparative genomic hybridization (array CGH) and whole exome sequencing (WES) to determine the EZH2 copy number status to evaluate whether clinical effect observed in the EZH2 WT population is due to the presence of EZH2 amplifications (copy number gains; CNG) to rule out a potential inflated response due to patients with CNG in WT group. Clarify how patients with CNG vs patients with no CNG or EZH2 mutations will be incorporated into the biomarker-adaptive design.
- b. In addition, we recommend that you demonstrate that the prevalence of EZH2 CNG is not greater than the described prevalence in literature if you intend to pursue an indication for the WT population.
- c. Provide additional rationale for your plan to cap the number of patients with EZH2 mutations to 15% since rates of 28% and 27% of SNV EZH2 mutations have been reported ^{1,2}.

¹Huet, et. Al.,2017 EZH2 alterations in follicular lymphoma: biological and clinical correlations. Blood Cancer Journal (2017) 7

<https://www.nature.com/articles/bcj201732>

² Bodor, et.Al.,2013 EZH2 mutations are frequent and represent an early event in follicular lymphoma. Blood, 31 OCTOBER 2013

<http://www.bloodjournal.org/content/bloodjournal/122/18/3165.full.pdf>

Discussion: The Agency reiterated the recommendation that the Sponsor conduct two randomized trials to verify the clinical benefit of tazemetostat in follicular lymphoma. At this time, the Agency could not agree to the proposed single randomized trial to support regular approval due to the following major concerns with the trial design and assumptions:

1. The Agency does not consider the proposed trial to be feasible within a reasonable timeframe for the second-line follicular lymphoma population. The plan to require 135 PFS events in 150 patients in the EZH2 mutated population and 360 PFS events in 400 patients in the total population (>90% of events in the population analyzed) is not feasible for follicular lymphoma population which has a long natural history. The Agency cited the results of the AUGMENT trial and noted the PFS event rates and follow-up time in that trial.
2. The Agency recommended that for the interim analyses, the EZH2 MT population should be tested first followed by testing of the total or WT population.
3. The Agency expressed concerns regarding the use of a difference in the median PFS for the interim analysis given the immaturity of median PFS at the interim analysis timepoints. The Agency also expressed concern that the planned interim analysis may not provide information until the trial is nearly completely enrolled.
4. The Agency clarified that there was no objection to the use of ORR as a basis for the interim analyses. The Agency recommend using data-supported thresholds for differences in ORR that would result in stopping the trial for futility or in enrichment for the EZH2 MT population.
5. The Agency recommended that the Sponsor consider potential disparate efficacy results in the EZH2 MT and WT populations and evaluate the robustness of the proposed study design to handle this issue. The Agency noted a potential scenario where the PFS benefit may be positive in the EZH2 MT population, and may be neutral or negative in the EZH2 WT population.

6. Given the blinded, randomized nature of the trial, the Agency expressed the acceptability of investigator-assessed PFS for the primary analysis. The Agency recommended that the Sponsor should consider the following with regards to investigator-assessed PFS:
 - a. The trial should have an auditing procedure to verify the investigators' assessment of progression are consistent with your proposed response criteria.
 - b. The clinical trial should include a standard imaging charter.
 - c. Assessment of response should be standardized amongst investigators.
 - d. The impact that inadvertent unblinding due to toxicity in the study arm should be considered.
7. The Sponsor indicated that there is a pre-submission meeting with CDRH for the EZH2 mutation test, a real-time allele-specific PCR test (cobas, EZH2 Mutation test). The Agency indicated that a diagnostic device for EZH2 testing should be available at the time of the first sNDA submission for a FL indication. The Sponsor indicated that results of copy number gain (CNG) abnormalities in the WT population and the impact of CNG on ORR would be discussed with the Agency at the pre sNDA meeting in Q3 2019.
8. The Agency noted that secondary malignancies have been described with the treatment backbone of lenalidomide and rituximab and expressed concern whether tazemetostat may increase this risk.

Question 1b: *The futility design with non-binding rule will preserve the type-I error, and the decision to stop the stage 1 and initiate the stage 2 of the study will be recommended by an independent data monitoring committee while the Sponsor will remain blinded to the interim results. Does the Agency agree with the proposed futility monitoring approach?*

FDA Response to Question 1b:

Non-binding futility design based on stage 1 is generally acceptable to preserve the type-1 error.

Explain how continuous futility monitoring for ORR will be implemented, given that the ORR for lenalidomide and rituximab for patients with FL was 80% based on the results of the AUGMENT trial.

Discussion: Refer to items 2-4 in Discussion to Question 1a.

Question 2: *Does the Agency agree with the proposed PK analysis plan to support the proposed confirmatory phase 3 study (EZH-302)?*

FDA Response to Question 2: Yes, your proposed PK analysis plan appears to be reasonable to support the proposed confirmatory phase 3 study. However, the acceptability of your population PK and exposure-response analyses will be a review issue.

Additionally, you've provided two different PK sampling plans in the protocol synopsis (Page 40) and Schedule of Visits and Procedures (Table 1). Please clarify.

Discussion: No discussion occurred.

Written Response Only Questions (3-8)

Discussion: No discussion occurred for Questions 3-8.

Question 3: *At the time of the planned FL NDA submission, the ES NDA will be under DOP2 review (see Table 1 for target timelines). Epizyme proposes to use the ES original accelerated approval NDA submission version of the label with revision-marked FL information and to submit an updated version with the approved ES label after the ES NDA is approved. Does the Agency agree with the proposal?*

FDA Response to Question 3:

Your proposal regarding the plan for the label submission is reasonable.

Question 4: *Based on the notion that the chemistry, manufacturing, and controls (CMC) and nonclinical reports included in the ES NDA cover both the ES and the FL indications, Epizyme proposes that the planned FL NDA cross-reference the ES NDA Module 3 and Module 4 for CMC information and nonclinical reports, respectively. Does the Agency agree with the proposal?*

FDA Response to Question 4:

Your proposal is acceptable.

Question 5a: *Does the Agency agree with the proposed Module 2 format?*

FDA Response to Question 5a:

Yes, we agree.

Question 5b: *Does the Agency agree with the proposal to harmonize the Summary of Clinical Safety (SCS) cutoff date with that for ES NDA's four-month safety update report (May 2019)?*

FDA Response to Question 5b:

No, a later safety cutoff date will be required for the proposed sNDA to support a follicular lymphoma indication. Revise your plan to include a 120-day safety update with a cutoff date no earlier than September 2019 for a December 2019 submission.

Question 6: *Does the Agency agree with the proposed Module 5 format for the planned FL NDA?*

FDA Response to Question 6:

No. You did not include bioanalytical reports and analytical methods in Module 5.3.1 Report of Biopharmaceutic Studies. The other components of Module 5 are acceptable.

Question 7: *During preparation for the ES NDA, DOP2 requested (see IND 124608 Type C Meeting Minutes, dated 14 January 2019) the following for narratives and case report forms (CRF):*

- *Narratives and CRFs for all deaths occurring during study treatment and up to 30 days after treatment discontinuation, regardless of cause*
- *Serious adverse events regardless of relatedness occurring during study treatment and up to 30 days after treatment discontinuation*
- *All adverse events leading to treatment discontinuation*
- *Withdrawals due to reasons other than disease recurrence or adverse events*

Does the Agency agree that Epizyme should use the same criteria for the planned FL NDA?

FDA Response to Question 7:

No, in addition to the narratives for and CRFs for the conditions listed for the ES NDA, for the FL sNDA, also include narratives for any AEs of second primary malignancy or myelodysplastic syndrome.

Question 8: *Does the Agency agree that the proposed SCE can satisfy the requirement for an ISE and that a separate ISE is not necessary?*

FDA Response to Question 8: An integrated summary of efficacy (ISE) is a required component of the application. The summary of clinical efficacy can serve as the ISE provided the data can be included within the space limitation of the SCE. In this situation, it is acceptable for the ISS to include a page with a cross-reference to the summary of clinical efficacy in the ISE. We refer you to the following guidance: Guidance for Industry: *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).¹

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to [FDA.gov](https://www.fda.gov).²

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD & C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants³ to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to [FDA.gov](https://www.fda.gov).⁴

1

<https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCDE/ucm544641.htm>

2

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

³ See the guidance for industry "Formal Meetings Between the FDA and Sponsors or Applicants."

⁴ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

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DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.⁵

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,⁶ as well as email access to the eData Team (cdere-data@fda.hhs.gov) for specific questions related to study data standards.

Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁷ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan

⁵ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁶ <https://www.fda.gov/media/88173/download>

⁷ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

U.S. Food and Drug Administration

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(see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.⁸ For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide⁹ (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.¹⁰ When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.¹¹

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources¹² and the CDER/CBER Position on Use of SI Units for

⁸ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

⁹ <https://www.fda.gov/media/88173/download>

¹⁰ <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹¹ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

¹² <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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Silver Spring, MD 20993

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Lab Tests website.¹³

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.¹⁴

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.¹⁵

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.¹⁶

¹³ <https://www.fda.gov/media/109533/download>

¹⁴ <http://www.fda.gov/ectd>

¹⁵ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

¹⁶ <https://www.fda.gov/media/85061/download>

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

- (1) Study phase
- (2) Statement of whether the study is intended to support marketing and/or labeling changes
- (3) Study objectives (e.g., dose finding)
- (4) Population
- (5) A brief description of the study design (e.g., placebo or active controlled)
- (6) Specific concerns for which you anticipate the Division will have comments
- (7) For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection*

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of Race and Ethnicity Data in Clinical Trials for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

The Sponsor will discuss the results of the Copy Number Gain analysis with CDER and CDRH.

5.0 ACTION ITEMS

Action Item/Description	Owner
The Sponsor will provide an updated synopsis and draft protocol/statistical analysis plan for FDA's review prior to the Stage 2 of study EZH-302.	Sponsor

6.0 ATTACHMENTS AND HANDOUTS

Email correspondence on July 11, 2019, containing the presentation titled "IND 124025 Type B EOP Meeting".

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 124025

MEETING MINUTES

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

Dear Dr. Jiang:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tazemetostat.

We also refer to the meeting between representatives of your firm and the FDA on December 19, 2018. The purpose of the meeting was to discuss the clinical development of tazemetostat for relapsed or refractory follicular lymphoma under an accelerated pathway, gain agreement on the treatment effect of tazemetostat and discuss the trial design for the Phase 3 study.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Thomas Iype, Regulatory Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: December 19, 2018; 11:00 AM – 12:00 PM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Sponsor/Applicant Name: Epizyme, Inc.
Application Number: IND 124025
Product Name: Tazemetostat
Indication: Tazemetostat is indicated for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least two prior systemic therapies.

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Thomas Iype, PharmD, RPh

FDA ATTENDEES

Division of Hematology Products

Albert Deisseroth, MD, PhD, *Supervisory Associate Division Director*
R. Angelo De Claro, MD, *Clinical Team Leader*
Margret Merino, MD, *Clinical Reviewer*

Division of Biostatistics V

Jingjing Ye, PhD, *Biometrics Team Leader*
Haiyan Chen, PhD, *Biometrics Reviewer*

Center for Devices and Radiological Health (CDRH)

Division of Molecular Genetics and Pathology/Molecular Genetics Branch

Donna M. Roscoe, PhD, *Branch Chief*
Fengmin Li, PhD, *Reviewer*

SPONSOR ATTENDEES

Deyaa Adib, MD, *Interim NHL Medical Director, Clinical Research*
Shefali Agarwal, MBBS, PH, MS, *Chief Medical Officer*
Robert Bazemore, *President and CEO*
Huiping Jiang, PhD, *Vice President, Regulatory Affairs*

Neil Michaud, PHD, *Director, Translation Medicine*
Kate Newberry, PhD, *Associate Director, Clinical Research*
Pamela Strode, MS, *Senior Vice President, Regulatory Affairs and Quality Assurance*
Jay Yang, PhD, *Vice President, Biostatistics*
Aldert Blank, *Director, Program Management*
Vikram Kansra, PhD, *Clinical Pharmacokinetics*
Michael Thomenius, PhD, *Clinical Translational Lead*

John Pagel, MD, PhD, *Chief, Hematologic Malignancies and Director of Stem Cell Transplantation, Swedish Cancer Institute*

(b) (4)

1.0 BACKGROUND

Epizyme, Inc. proposes to utilize efficacy data from the follicular lymphoma cohorts of a Phase 2 study (E7438-G000-101) to support an accelerated approval in adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies. The ongoing Phase 2 portion is a single arm study that utilizes tazemetostat 800 mg twice a day with a primary objective to determine the objective response rate (complete response + partial response) in relapsed or refractory patients with enhancer of zeste homolog 2 (EZH2) gene mutation positive or negative (wild type) follicular lymphoma. Epizyme, Inc. has also conducted two retrospective studies to analyze whether the EZH2 mutation is a beneficial prognostic factor in patients that have received 3 plus lines of therapy. The Sponsor seeks alignment with FDA on the accelerated pathway, the treatment effect of tazemetostat that meets an unmet medical need, and preliminary guidance for a clinical trial that could potentially support a regular approval.

2.0 DISCUSSION

Question 1: *The data from this external multi-center natural history study EZH-107 (see Appendix 3 for a preliminary report), in addition to natural history data from study E7438-G000-101 (Appendix 2) provide confirmation that EZH2 mutation is not a positive prognostic factor in patients with 3L+ FL. Therefore, the clinical activity observed in the patients with R/R FL and the responses observed in the mutation positive and WT cohorts in study E7438-G000-101 can be attributed to tazemetostat. Does the Agency agree?*

FDA Response to Question 1:

The Agency notes that the natural history study EZH-107 study report and datasets could provide the context necessary to evaluate the clinical activity of tazemetostat monotherapy in the mutation positive and WT cohorts in study E7438-G000-101. However, additional details are needed on the definition of EZH2 WT (wild-type status), and address potential misclassification of certain patients as EZH2 WT in the natural history study and ongoing or planned clinical tazemetostat clinical trials.

The meeting package describes screened specimens from patients using the RMS test which is designed to identify 7 specific point mutations within EZH2 (Y646N, H, F, S, C, A682G and A692V). The term “wild-type” refers to the absence of detection of the above-specified

mutations. While these single nucleotide variants (SNVs) represent the majority of mutations detected in the EZH2 in B-cell lymphomas, it is not clear to what extent other EZH2 pathogenicity may be represented in the wild-type group.

Huet et al. (Blood Cancer J. 2017 Apr 21;7[4]:e555) indicated that 29% (46/159) of patients with follicular lymphoma harbored an alteration in the EZH2 gene that was a SNV and 15% (23/159) were EZH2 copy number amplifications. This is consistent with other literature reporting EZH2 gains in 20-30% of patients. The gene insertion and copy number gain cannot be detected by the EZH2 assay and may have been classified with the “wild type” group.

The Huet 2017 article also indicated that EZH2 genetic alterations were an independent factor associated with progression free survival. Kaplan-Meier curves are presented in the article demonstrating differences in PFS outcomes with and without EZH2 mutations and gains, and no alterations. Therefore, it is possible that the presence of subjects with EZH2 copy number gains are contributing to the efficacy observed in the “wild-type” group, leading to similarity in outcomes between EZH2 mutant (MT) and EZH2 WT in the natural history study.

Discussion:

The Sponsor provided clarification on the mechanism of action of tazemetostat for WT EZH2. The Agency agrees with the Sponsor’s proposal to test archival samples from all patients for copy number gain. The Agency suggested that Sponsor discuss with CDRH regarding this testing strategy.

The Agency recommended that the Sponsor adequately describe the population in terms of EZH2 mutation and amplification status as this information would be critical for labeling.

The Agency clarified that concerns regarding the definition of wild type would be addressed by the steps outlined above.

The Agency acknowledged that the Sponsor’s additional efforts to provide clinical context for the activity of tazemetostat through use of the natural history study and additional market research data. This could be considered as supportive data with the application.

The Agency noted that occurrence of responses in patients who have progressed after a previous regimen that these responses would be attributed to the new therapy that was initiated.

Question 2a: Does the Agency agree that the proposed benefit/risk of tazemetostat is adequate to support a registration submission for the proposed indication for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least two prior systemic therapies?

FDA Response to Question 2a: Your proposed approach for initial registration based on a single-arm trial would be more consistent with an accelerated approval pathway, which requires the drug provides a meaningful advantage over available therapies. As you noted in Appendix 11 of your meeting package, there are multiple ongoing clinical trials (page 261-262) in relapsed or refractory follicular lymphoma. The definition of available therapy that would be applicable for your application will be based on the time of regulatory action for your application. Hence, it will be important to capture all prior therapies for your patient population. The Agency notes that the prior therapies that have been coded (page 81 of meeting package) mainly reflect rituximab and cytotoxic chemotherapy, and lack information on prior exposure to therapies such as lenalidomide, ibrutinib, PI3K inhibitors, BCL2 inhibitors, other anti-CD20 antibodies, etc.

Discussion: No discussion occurred

Question 2b: *If the answer to Question 2a is “yes”, does the Agency agree that combined data from the fully enrolled FL MT (N = 45) and FL WT (N = 54) cohorts for a total of ~100 patients could form the primary basis for the registration submission?*

FDA Response to Question 2b: Data from a total of 100 patients with FL with at least 45 FL MT and 54 FL WT may be adequate to support a submission provided that there is at least 12 months of response follow up for all responders. The Agency also recommends submission of safety analyses and datasets for tazemetostat monotherapy across the entire development program.

We recommend that you consult with CDRH to develop a companion/complementary diagnostic given the different response rates noted in the EZH2 mutated vs WT population as this may be important information to convey to prescribers and patients and could be included in the United States Prescribing Information (USPI).

Refer also to response to question 1 regarding potential misclassification of certain patients as EZH2 WT.

Discussion:

The Sponsor provided an update for the duration of response (DOR) follow-up for the WT population (n=54), which is beyond 2 years for all responders. This follow-up duration is acceptable to the Agency.

Regarding the MT population, the Sponsor notes that 3/4 of the population would have at least 12 months of DOR follow-up (n=45) at the time of NDA submission. The Agency would be willing to discuss the proposed data cut-off for this population at the time of the pre-NDA meeting. The Agency recommended that the Sponsor include detailed information on projected follow-up for safety and efficacy in the meeting package.

The Agency stated that for regulatory decision-making based on single arm trials, independent review committee (IRC) assessment is required for evaluation of the efficacy endpoints.

The Agency recommended that IRC-assessed efficacy endpoints should be included with the pre-NDA application meeting package.

Question 3: *Does the Agency agree that the planned phase 3 Study EZH-302 with safety run-in could serve as the confirmatory study to verify the clinical benefit of tazemetostat and to satisfy a postmarketing requirement to support a full approval in R/R FL patients?*

FDA Response to Question 3: The Agency recommends that the Sponsor conduct more than one randomized trial to verify the clinical benefit of tazemetostat, due to differences observed in clinical activity in patients with WT or MT EZH2 status. This will also allow for a more comprehensive characterization of the role of tazemetostat for the treatment of relapsed or refractory FL, specifically as monotherapy or in combination, and in EZH2 WT and MT subgroups.

The first randomized trial could be tazemetostat monotherapy versus an active control in patients with MT EZH2 relapsed or refractory FL with a primary endpoint of IRC-assessed PFS.

For the second trial, the proposed EZH-302 evaluating tazemetostat in combination with rituximab and lenalidomide based on a PFS endpoint appears reasonable. The ultimate decision regarding whether the study results would support conversion to full approval will be a review issue.

We have the following comments regarding EZH-302:

Clinical/Statistical

1. The final protocol should be submitted to the Agency for review and any deficiencies addressed prior the first patient enrollment
2. We do not agree with your safety run in phase to evaluate 400mg and then 800mg of tazemetostat in combination with R2. You should evaluate 600mg PO BID prior to escalating to 800mg.
3. Clarify whether the trial would be enriched for EZH2 MT or minimum percentage with EZH2 MT to be randomized.
4. The primary endpoint of PFS should be IRC assessed.
5. Clarify the frequency of response assessments during and after study therapy.
6. We recommend central assessment of EZH2 status for stratification and analyses. EZH2 status assessment should include copy number of amplification.
7. Clarify if the protocol will include PFS and response rates by EZH2 status as secondary analysis.

Clinical Pharmacology

8. In the Safety Run-In, reduce the dose of lenalidomide to 10 mg once daily on Days 1 to 21 for patients with creatinine clearance < 60 mL/min as consistent with that proposed in the Phase 3 portion of the trial.

9. Provide justification for selection of the proposed dosing regimen in the Phase 3 portion of the trial. Prior to initiating the Phase 3 portion of Study EZH-302, pool available clinical pharmacokinetic, pharmacodynamic, activity and safety data, as well as nonclinical pharmacology data, to conduct integrated dose-response and exposure-response analyses for dose optimization of tazemetostat in combination with lenalidomide and rituximab.
10. Evaluate the potential for a pharmacokinetic interaction between tazemetostat and lenalidomide.
11. Include a plan to perform exposure-response analyses for efficacy, safety, and pharmacodynamic markers.
12. Consider removing the exclusion criterion with regards to QTcF if data supports that tazemetostat does not have the potential for QT prolongation.

Finally, the Agency notes a potential scenario wherein EZH-302 demonstrates clinical benefit that is different between EZH2 WT and MT populations, with a possibility that all or most of the clinical benefit is derived in the population EZH2 MT. Discuss how you plan to address this potential scenario.

Discussion: No discussion occurred

Question 4: *The current IND 124025 is dedicated specifically to studying tazemetostat in NHL. As we develop the phase 3 Study EZH-302, does the Agency agree that it is acceptable to conduct this study under the currently effective IND 124025 for US sites?*

FDA Response to Question 4: Yes, your proposal to submit study EZH-302 to IND 124025 is acceptable.

Discussion: No discussion occurred

Additional Clinical Pharmacology Comments:

During clinical development of tazemetostat, a drug-drug interaction (DDI) study with a strong CYP3A inhibitor may need to be conducted.

3.0 OTHER IMPORTANT INFORMATION

FOR ONCOLOGY APPLICATIONS ONLY

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those

applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR: <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm>. In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid: <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm>

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and

any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For the latest version of the molecular target list, please refer to <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm>.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>.

In addition, you may contact the OCE Subcommittee of PerC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized

format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The [FDA Study Data Technical Conformance Guide](#) (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the [FDA Study Data Standards Resources](#) web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at

<https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf>) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

The impact of copy number gains on the WT population is to be discussed after archival samples from all patients are tested.

5.0 ACTION ITEMS

There are no action items other than the suggestion to request a Pre-NDA meeting.

6.0 ATTACHMENTS AND HANDOUTS

Reference is made to your email send on December 16, 2018 containing the presentation below.

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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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