

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

220305Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 142028

MEETING MINUTES

Kura Oncology, Inc.
Attention: Matthew Kelly
Vice President, Regulatory Affairs
2 Seaport Lane, Suite 8A
Boston, MA 02210

Dear Matthew Kelly:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ziftomenib, KO-539.

We also refer to the video conference between representatives of your firm and the FDA on February 3, 2025. The purpose of the meeting was to obtain Agency feedback on the planned New Drug Application (NDA) submission for ziftomenib, primarily based on top-line results from KO-MEN-001 Phase 2, for the treatment of adults with relapsed and/or refractory (R/R) acute myeloid leukemia (AML) with nucleophosmin 1 (NPM1) mutations.

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

If you have any questions, contact Tawanna Stokes, Regulatory Information Specialist, at 301-796-2927 or via e-mail to tawanna.stokes@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Cara Rabik, MD, PhD
Clinical Team Leader
Division of Hematologic Malignancies I
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: February 3, 2025, 9:00am ET
Meeting Location: Videoconference]

Application Number: IND 142028
Product Name: Ziftomenib
Indication: Ziftomenib is proposed for the treatment of adult patients with relapsed and/or refractory (R/R) acute myeloid leukemia (AML) with nucleophosmin 1 (NPM1) mutations
Sponsor/Applicant Name: Kura Oncology, Inc.
Regulatory Pathway: 505(b)(1)

Meeting Chair: Cara Rabik, MD, PhD, Clinical Team Leader
Meeting Recorder: Tawanna Stokes, Regulatory Information Specialist

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/Division of Hematologic Malignancies I (DHMI)
Kelly Norsworthy, MD, Deputy Division Director
Cara Rabik, MD, PhD, Clinical Team Leader
Joseph Wynne, MD, PhD, Clinical Reviewer

Office of Regulatory Operations (ORO)/Division of Regulatory Operations for Oncologic Diseases/Hematologic Malignancies I
Amy Baird, Chief, Project Management Staff
Tawanna Stokes, BA, Regulatory Information Specialist

Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Nan Zheng, PhD, Clinical Pharmacology Team Leader

Office of Clinical Pharmacology/Division of Cancer Pharmacology II
Dapeng Cui, Senior Pharmacokineticist

Office of Biostatistics/Division of Biometrics IX
Jonathon Vallejo, PhD, Biometrics Team Leader
Xin Wang, PhD, Biometrics Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products I, Branch II
Shalini Anand, PhD, Senior Pharmaceutical Quality Assessor
Damien Duveau, PhD, Pharmaceutical Quality Assessor

Office of Product Quality/Division of Biopharmaceutics/Branch I

Anitha Govada, PhD, Biopharmaceutics Lead/SPQA

Alaadin Alayoubi PhD, Biopharmaceutics Reviewer

Center for Devices and Radiological Health (CDRH)/Office of Product Evaluation and Quality (OPEQ)/Office of In Vitro Diagnostics and Radiological Health (OHTV)/Division of Molecular Genetics and Pathology (DMGP)/Molecular Genetics Branch (MGB)

Victoria Hill, PhD, Scientific Reviewer

SPONSOR ATTENDEES

Mollie Leoni, MD, Chief Medical Officer, Kura Oncology, Inc. (Kura)

Matt Kelly, MS, Vice President, Regulatory Affairs, Kura

David Reed, MBA, Senior Director, Regulatory Affairs CMC, Kura

Caitlin Skenyon, PharmD, Associate Director, Regulatory Affairs, Kura

Roger Bakale, PhD, Senior Vice President, Manufacturing and Supply Chain, Kura

Craig Bowe, Executive Director, CMC and Technical Operations, Kura

Maureen Clancy, MBA, Vice President, Global Program Leadership, Kura

Harris Soifer, PhD Vice President, Precision Medicine, Kura

Daniel Corum, PhD, Executive Director, Clinical Development, Kura

Amitava Mitra, PhD, Executive Director, Clinical Pharmacology, Kura

Ying Tian, PhD, Executive Director, Biometrics, Kura

Zijing Zhang, PhD Senior Director, Biostatistics, Kura

Mitsuhiko Odera, Director, Development, Kyowa Kirin Co., LTD.

Gary Trewartha, Director, Global Regulatory Affairs, Kyowa Kirin International

1.0 BACKGROUND

The purpose of this meeting is to obtain Agency feedback on the planned New Drug Application (NDA) submission for ziftomenib, a selective small molecular menin inhibitor. The primary efficacy claim will be based primarily on the Phase 2 top-line results from KO-MEN-001, with a proposed indication for the treatment of adults with relapsed and/or refractory (R/R) acute myeloid leukemia (AML) with nucleophosmin 1 (NPM1) mutations.

The Sponsor submitted the topline efficacy results from KO-MEN-001 as part of the background materials for this submission, which are presented below.

Table 10 Primary Efficacy – Remission Rates and Duration

Endpoint	KO-MEN-001 Phase 2 mITT (n=92)	KO-MEN-001 Part 1b EAS (n=20)	Pooled (N=112)
CR/CRh ^a , n (%)	20 (21.7)	7 (35.0)	27 (24.1)
95% CI	(13.8, 31.6)	(15.4, 59.2)	(16.5, 33.1)
P-value	0.0058	N/A	N/A
Median DOR ^b (months)	3.7	5.6	3.7
95% CI	(1.9, 7.4)	(0.6, 8.1)	(1.9, 7.7)
CR ^c , n (%)	13 (14.1)	7 (35.0)	20 (17.9)
95% CI	(7.7, 23.0)	(15.4, 59.2)	(11.3, 26.2)
Median DOR ^d (months)	3.7	5.6	3.7
95% CI	(2.8, 7.4)	(0.6, 8.1)	(1.9, 7.7)
CRh ^e , n (%)	7 (7.6)	0	7 (6.3)
95% CI	(3.1, 15.1)	(0, 16.8)	(2.5, 12.5)
Median DOR ^f (months)	1.9	N/A	1.9
95% CI	(1.0, NE)	N/A	(1.0, NE)

Source: Table 10, meeting package (page 27).

In addition, the Sponsor stated that 19.5% of patients in the mITT who were transfusion-dependent at baseline became independent of red blood cell and/or platelet transfusion.

FDA sent Preliminary Comments to Kura Oncology Inc. on January 28, 2025.

2.0 DISCUSSION

2.1 Clinical/Statistics

Question 1: Overall, ziftomenib continues to be well-tolerated and the benefit-risk supports use in patients with relapsed/refractory AML with NPM1 mutations. Does the Agency agree that the results from the pivotal Phase 2 KO-MEN-001 study are adequate to support the submission and review of a New Drug Application (NDA) for traditional approval in the proposed indication?

FDA Response to Question 1:

Yes. Your topline results appear generally adequate to support submission and review of a New Drug Application. Whether the efficacy and safety data are sufficient to support your proposed indication will be determined during our review of the application. We have the following additional comments:

- a. In AML, for nonmyelosuppressive drugs given without intent to cure, durable CR/CRh and evidence of transfusion independence (TI: 56-day or 112-day) have been used to support marketing applications. Adequate follow-up is needed to establish the durability of the response and TI rates. We are concerned about the low rates of TI, short DoR, and short median follow-up in KO-MEN-001.
- b. Include in the NDA submission the following:

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- i. Patient level data regarding prior treatments (including those with other targeted therapies) and comutations for which there are potential alternative therapies.
 - ii. A summary of treatment exposure, including at least median, mean, and range.
 - iii. A summary of disease status at the time of enrollment on study (e.g., primary refractory versus untreated relapsed versus refractory relapsed AML).
- c. We reiterate the recommendations in the Type C meeting minutes dated 01 December 2023 regarding the evaluation of the potential needs for conducting dedicated hepatic impairment (HI) and cytochrome P450 (CYP) enzyme- and/or transporter- mediated DDI trials. The acceptability of your proposed clinical pharmacology approaches without the dedicated HI and/or clinical DDI study results to inform labeling recommendations will be determined during NDA review. Also refer to Additional Clinical Pharmacology Comments for recommendations on preparation of clinical pharmacology sections of the submission.

Discussion: No discussion occurred.

Question 2: Does the Agency agree with the proposed cutoff date and content for the Safety Update, including the potential to submit 90 days after the NDA submission?

FDA Response to Question 2:

Yes, we agree with the content and timing of the proposed safety update. Ensure that you include the safety update report (SUR) document; updated tables, listings, and figures; updated integrated dataset; and updated narratives from KO-MEN-001.

Discussion: The Sponsor commits including updated tables, listings, and figures; an updated integrated dataset; and updated narratives from KO-MEN-001 to the SUR. The NDA submission is planned for submission in mid-April, with a planned data cutoff date for the SUR of March 28, 2025. However, the submission of the NDA may vary by 1-2 weeks, and the Sponsor is requesting a 1-2 week period of flexibility for the data cutoff date for the SUR as well. The FDA stated that this 1-2 week period of variability around March 28, 2025, for the SUR data cutoff date appears reasonable.

Question 3: Does the Agency agree with providing updated efficacy data with the Safety Update?

FDA Response to Question 3:

While we are not opposed to your submission of updated efficacy data for transfusion independence and duration of response with the safety update, please note that the review will focus on the primary efficacy analysis as stipulated in the SAP (submitted to the IND in SDN 241).

Discussion: No discussion occurred.

2.2. CMC

Question 4: *For the registrational drug product, the Sponsor intends to provide 6 months of accelerated condition (40°C / 75% RH) stability data and 12 months of long term (25°C / 60% RH) stability data in the original NDA submission. Does the Agency agree that updated long-term 18-month stability data on the registrational batches and additional data collected from the (b) (4)-count configuration can be submitted no later than 90 days prior to the PDUFA date?*

FDA Response to Question 4:

Your proposed approach to submit twelve (12) months of long-term and six (6) months of accelerated stability data for the drug product registration batches in the original NDA submission appears reasonable. Also, submit the available stability data for Ziftomenib (KO-539) capsules in the (b) (4)-count configuration at the time of NDA submission. Submit the additional stability data to the NDA as soon as the data are available but no later than ninety (90) days prior to the PDUFA goal date. The final determination regarding acceptability of the drug product stability data and proposed shelf life will be made upon review of the data submitted to the NDA.

Discussion: No discussion occurred.

Question 5: *The Sponsor is implementing a plan to address recently received feedback on the proposed dissolution method for ziftomenib drug product. Does the Agency agree for any updated Module 3 sections related to potential modifications of the dissolution method to be submitted within 60 days of the original NDA filing?*

FDA Response to Question 5:

Your proposal to update Module 3 sections related to the dissolution method for the proposed drug product Ziftomenib 200 mg Capsule within 60 days of the original NDA filing is acceptable. The update should include complete dissolution data/information to address the Agency's comments communicated to you on December 2, 2024, regarding optimization of the proposed dissolution method for your drug product. The final determination of acceptability of the dissolution method for quality control of the proposed drug product will be made upon review of the data submitted.

Discussion: No discussion occurred.

2.3 Regulatory

Question 6: Does the Agency agree that the content of the NDA will constitute a complete application for the proposed indication?

FDA Response to Question 6:

All sections proposed in the Table of Contents appear to be acceptable. From a technical perspective, please refer to the Comprehensive Table of Contents Headings and Hierarchy for more details at <https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/ectd-submission-standards-ectd-v40-and-regional-m1>. See also the response to Question 8 and Section 3.0, below, for the subheading: "Efficacy Datasets for Acute Leukemia Drug Applications."

Please ensure that you also include protocols and amendments for all studies. The adequacy of the data for filing will be determined following our review of your NDA submission.

Discussion: No discussion occurred.

Question 7: Ziftomenib has been granted Breakthrough Therapy Designation and is therefore eligible for priority review. Can the Agency comment on the applicability of priority review as it may apply to the NDA?

FDA Response to Question 7:

The Agency determines whether an application qualifies for priority review at the time of filing. Please provide a Request For Priority Review Designation in bold uppercase letters in your cover letter and include a concise summary of the information that supports the priority review designation request. See Appendix 1, Section C of the FDA Guidance for Industry | [Expedited Programs for Serious Conditions – Drugs and Biologics](#) for additional information.

Discussion: No discussion occurred.

Question 8: QIAGEN, Kura's companion diagnostic (CDx) partner, will not meet the contemporaneous PMA submission timeline because analytical validation studies are on hold due to a technical issue that impacts robustness and performance of the intended NPM1 CDx. Does the agency agree to consider a Post Marketing Requirement/Commitment (PMC) for the accompanying CDx device submission because of the clinical benefit that ziftomenib has demonstrated in an unmet need population with access to standard of care NPM1 testing?

FDA Response to Question 8:

The acceptability of the proposal to market ziftomenib for the proposed patient population without a CDx will be a review issue. We have the following comments:

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- a. We note that patients in KO-MEN-001 were enrolled based on local testing of NPM1. It is unclear whether the central banked sample was tested for confirmation of the local diagnosis. Please clarify whether this central testing occurred. If central testing was performed, ensure that you include the following information on the central test:
 - i. A statement of the intended use.
 - ii. The specific test method (including instruments, reagents, and specimen handling).
 - iii. Confirmation that the lab has a process in place for reagent control.
 - iv. A brief discussion of how the test method was validated analytically for each specimen type.
 - v. A statement of the performance obtained for accuracy and analytical sensitivity.
- b. Please plan to submit the local NPM1 testing results and the central laboratory testing results (if available per 8.a, above). If central testing was performed, for any patients with discordant NPM1 mutation results between central and local testing, please clarify whether the discordance was due to differences between the central and local assays with regard to detectable mutations.
- c. If the review concludes that the central assay (if available) is not analytically valid, or if a central assay was never performed, whether the local assay results can be relied upon to reflect the intended patient population will be a review issue. We strongly recommend that you plan to submit all available assay information (see 8.a.i-v, above) for the local site assays in addition to the results.
- d. Include a subgroup analysis of efficacy by NPM1 mutation site and by a quantitation of the mutation burden (e.g., VAF).
- e. Please clarify which NPM1 mutations will be detected by the proposed CDx.

Discussion: The Sponsor clarified that no central testing has occurred in order to preserve the samples for the future CDx. The FDA acknowledged this response and reiterated that the lack of central testing will be a review issue. The Sponsor will submit subject-level data for local testing and all available information on the local site assays into a spreadsheet that can be provided in PDF format. The Sponsor requested advice for where to locate this in the eCTD. The FDA responded that the Sponsor should submit the requested information as a PDF in Module 5.3.5 within the KO-MEN-001 study folder. In addition, the FDA also requested that the spreadsheet be submitted as a custom SAS dataset (within the AdAM folder).

The FDA asked the Sponsor if they had an estimated date for the

(b) (4)

(b) (4) submission.

(b) (4)

Additional Clinical Pharmacology Comments

1. Address the following questions in the Summary of Clinical Pharmacology:
 - a. What is the basis for selecting the recommended dosage used in the trials intended to support your marketing application? Include a description of the translational evidence, pharmacokinetics, safety, efficacy, dose-response/exposure-response and other information used to support dosage selection as described in the [Oncology Dosing Tool Kit](#).
 - b. What is the effect of ziftomenib on the QT/QTc interval?
 - c. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
 - d. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
 - e. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dosage modifications are recommended?
2. Apply the following advice in preparing the clinical pharmacology sections of the submission:
 - a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
 - b. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data with central tendency and intersubject/patient variability or median with maximum and minimum as appropriate.
 - c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Identify individual subjects with dosage modifications; the time to the first and subsequent dose reduction, interruption or discontinuation; and the reasons for dosage modifications in the datasets.
 - d. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers, safety and tolerability) relationships in the targeted patient population. Refer to Guidance for Industry for [population PK](#), [exposure-response relationships](#), and [pharmacometric data and models submission guidelines](#).
 - Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the

- non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.
- Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.
- e. When you submit your PBPK analyses report, please follow the recommendations described in FDA Guidance for Industry: [Physiologically Based Pharmacokinetic Analyses - Format and Content](#).
- f. When you submit your QT evaluation report, please include a completed version of the most recent “QT Evaluation Report Submission Checklist” located at the IRT website (<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt>).
3. The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, [Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format](#). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Agency noted that the Clinical, Statistical, Clinical Pharmacology, Nonclinical, and CMC components of the NDA submission appeared adequate.
- 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. It was concluded that a need for the REMS will be made during the review of the application and the Agency will notify the sponsor once a determination for a need for a REMS occurs.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted after the submission of the original application:
 - FDA reminds you to submit any additional stability data to the NDA as soon as the data are available but no later than ninety (90) days prior to the PDUFA goal date.
 - FDA reminds you to submit complete dissolution data/information to address the Agency's comments communicated to you on December 2, 2024, regarding optimization of the proposed dissolution method for your drug product no later than 60 days from the original NDA filing date.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA/BLA NUMBER: LATE COMPONENT - QUALITY

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

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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 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](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 the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

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 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

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

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>

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.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax	Email address
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U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

			number	
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁶ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁷. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

BIORESEARCH MONITORING INSPECTION PLANNING

Submit the data and information described in the guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* in your application.⁸ The data and information will be used to plan BIMO inspections, facilitate the timely identification of sites for inspection, and ensure that field investigators from the Agency have the information needed to conduct the 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). The guidance should be used in conjunction with the *Bioresearch Monitoring Technical Conformance Guide*, or BIMO TCG, when preparing the required data and information. The BIMO TCG provides more specific directions related to formatting and is updated routinely to provide current specifications, recommendations, and general considerations for preparing the data and information.

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

⁶ <https://www.fda.gov/media/84223/download>

⁷ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

⁸ <https://www.fda.gov/media/85061/download>

pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR.⁹ In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹⁰

REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products*.¹¹ For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

EFFICACY DATA SETS FOR ACUTE LEUKEMIA DRUG APPLICATIONS

To allow FDA to confirm the analyses of the treatment effect, the raw data supporting the efficacy endpoints should be submitted in the marketing application. We recommend that the data be organized in the datasets as follows:

- Provide the occurrence of all procedures in PR. Examples of procedures include, but are not limited to, marrow biopsy, marrow aspiration, lumbar puncture, tissues biopsies, transfusions, hematopoietic stem cell transplantation, and chimeric antigen receptor T cell or other effector cell therapy.
- Provide the results of the morphological examination of the marrow, including blasts by morphology and blasts by immunohistochemistry tests, in MI.
- The results of the complete blood count and differential, including peripheral blood blasts, should be submitted in LB and in LC in accordance with the *Study Data Technical Conformance Guide*.¹²
- Provide the occurrence and results of minimal residual disease (MRD) tests and chimerism tests in BS. See the FDA guidance "*Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of*

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>

¹¹ <https://www.fda.gov/media/124795/download>

¹² See the current version at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/study-data-technical-conformance-guide-technical-specifications-document>

Drug and Biological Products for Treatment"¹³ for details on the minimum data to submit.

- Provide the results of the morphological examination of the spinal fluid, including blasts by morphology and blasts by immunohistochemistry tests, in MI. Place the spinal fluid chemistry results in LB and LC. If collecting a categorization of CNS involvement (e.g., CNS-2), submit that in TR.
- Provide the results of other tests for extramedullary disease in TR. The location of physical exam or imaging findings of EMD should be identified in TU.
- Provide subsequent anti-leukemia therapies, including the preparative regimens for stem cell transplantation, in CM. Include a variable to identify the subsequent anti-leukemia therapy.
- Provide the remission status for each study visit in RS. Include an indicator of the evaluator (i.e., investigator, independent review committee, Sponsor's algorithm, etc.).
- Provide the time-to-event outcomes in ADTTE. Ensure that all data needed to derive the time-to-event outcomes are included in the SDTM domains as indicated above.
- Submit custom analysis datasets in the ADaM folder. See Appendix 3 of the FDA guidance "*Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment*"² for the list of data to include in the custom datasets.
- For patient-reported outcomes (PRO), see the general FDA technical specifications documents for these data types.¹⁴
- For Real-World Data (RWD) for use in efficacy analyses, the advice in the preceding sections applies with regard to the granular remission assessment data expected in the submission. For additional technical advice, see the general FDA guidances for RWD data standards.¹⁵

4.0 ISSUES REQUIRING FURTHER DISCUSSION

¹³ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

¹⁴ For example, "*Submitting Patient-Reported Outcome Data in Cancer Clinical Trials (November 2023)*".

¹⁵ For example, "*Data Standards for Drug and Biological Product Submissions Containing Real-World Data (December 2023)*".

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Kura Oncology Inc provided responses to the preliminary comments on January 30, 2025.

8 Pages have 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/

CARA A RABIK
02/03/2025 12:37:43 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 142028
Request Receipt Date	2/23/24
Product	Ziftomenib
Indication	For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with nucleophosmin (NPM1) mutations
Drug Class/Mechanism of Action	Menin inhibitor
Sponsor	Kura Oncology
ODE/Division	OOD/DHM1
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	4/23/24

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

- Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**
Treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with nucleophosmin (NPM1) mutations
- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**
☐ YES ☒ NO
- Was the BTDR submitted to a PIND?**
☐ YES ☒ NO
If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹? ☒ YES ☐ NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):
- i. Only animal/nonclinical data submitted as evidence ☐
 - ii. Insufficient clinical data provided to evaluate the BTDR
(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
 - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
 - v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

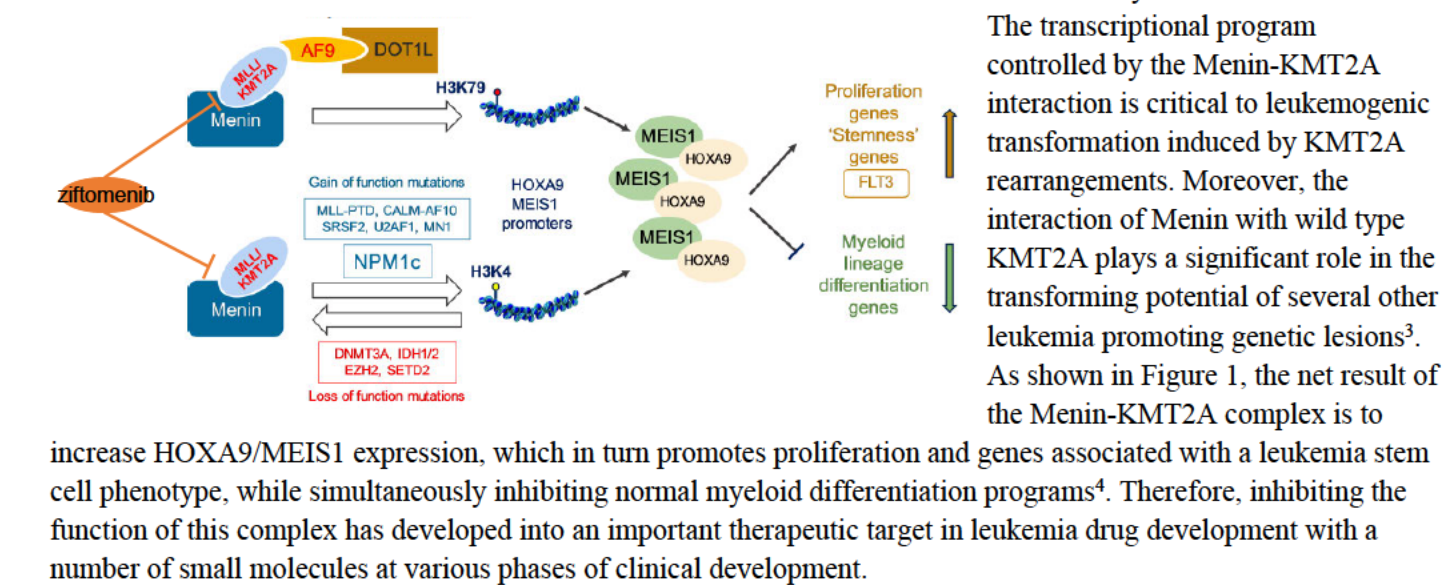
² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Ziftomenib is a small molecule that binds to the protein Menin, thereby inhibiting the interaction of Menin with the histone methyltransferase KMT2A.

Figure 1: Ziftomenib mechanism of action⁴

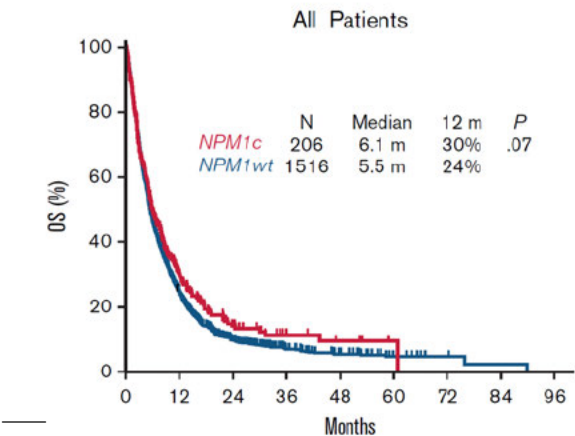


increase HOXA9/MEIS1 expression, which in turn promotes proliferation and genes associated with a leukemia stem cell phenotype, while simultaneously inhibiting normal myeloid differentiation programs⁴. Therefore, inhibiting the function of this complex has developed into an important therapeutic target in leukemia drug development with a number of small molecules at various phases of clinical development.

Ziftomenib disrupts the interaction between the KMT2A protein and Menin, repressing expression of the critical oncogenes that drive proliferation and survival of leukemic cells.

The potential of ziftomenib to treat cancers with KMT2A-r, as well as other genetic aberrations that confer Menin dependence, was demonstrated by the Sponsor in human tumor cell lines in vitro and subsequently confirmed and extended in CDX and PDX mouse models of leukemia. Overall, in vitro and in vivo studies demonstrated that

Figure 2:OS of R/R AML with NPM1-m or NPM1 wt⁹ ziftomenib is a potent, selective, and well-tolerated inhibitor of the Menin-MLL(KMT2A) interaction in both in vitro and in vivo models of both KMT2A-r and KMT2A-wt/NPM1-mutant (NPM1-m) AML. The focus of this BTDR is the use of ziftomenib to treat NPM1-m AML.



Mutation of NPM1 is the most frequent genetic alteration in AML, found in 2 to 8% of childhood AML and 27 to 35% of Adult AML^{5,6}. Mutations in exon 12 result in loss of binding to nucleoli such that the NPM1 protein is abnormally localized to the cytoplasm. NPM1-m AML has good initial response to chemotherapy, but prognosis is still guarded with approximately 50% long-term survival. However, in the

³ Thomas, X. Small Molecule Menin Inhibitors: Novel Therapeutic Agents Targeting Acute Myeloid Leukemia with KMT2A Rearrangement or NPM1 Mutation. *Oncol Ther* 12, 57–72 (2024). <https://doi.org/10.1007/s40487-024-00262-x>

⁴ Adapted from Sponsor Request for Breakthrough Therapy Designation, BTDR request submission, IND 142028/SDN177 page 6

⁵ Hollink IH, Zwaan CM, Zimmermann M, et al. Favorable prognostic impact of NPM1 gene mutations in childhood acute myeloid leukemia, with emphasis on cytogenetically normal AML. *Leukemia*. 2009;23(2):262-270. doi:10.1038/leu.2008.313

⁶ Thiede C, Koch S, Creutzig E, et al. Prevalence and prognostic impact of NPM1 mutations in 1485 adult patients with acute myeloid leukemia (AML). *Blood*. 2006;107(10):4011-4020. doi:10.1182/blood-2005-08-3167

relapsed/refractory setting, responses are short lived and OS appears similar to patients with wild-type NPM1 (NPM1 Wt) AML as seen in Figure 2⁹. There is no approved therapy targeting R/R NPM1 mutated AML.

Ziftomenib was granted Orphan Drug Designation on 7/22/2019 for treatment of acute myeloid leukemia, and Fast Track Designation on 8/14/2023 for treatment of patients with relapsed or refractory AML with nucleophosmin 1 (NPM1) mutation.

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.**

The efficacy endpoints presented by the sponsor were complete remission (CR), CR with partial hematologic recovery (CRh), and duration of remission (DOR), defined as the time from the date of first documented CR or CRh to the first documented relapse or death. These endpoints were prespecified to address an exploratory objective of the Phase 1a portion of the study and primary endpoints for the phase 1b and phase 2 components of the study to evaluate the efficacy of ziftomenib.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:**

For treatments of AML, overall survival (OS) and event-free survival (EFS) are endpoints considered to be direct measures of clinical benefits and have been used for regular approval. Durable CR is considered reasonably likely to predict long-term clinical benefit. CR+CRh with durability has been used for regular approval in the palliative setting for drugs that are nonmyelosuppressive and reasonably nontoxic.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.**

The Division would also consider a minimal residual disease-based endpoint such as "MRD-negative CR" as reasonably likely to predict clinical benefit when the assay used is analytically valid and the level of MRD used to define "negative" is justified.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

There are no approved drugs targeting the NPM1 mutation. The only FDA-approved therapy for R/R AML without specific genetic lesions is gemtuzumab ozogamicin (evaluated in the MyloFrance 1 study), where a CR rate of 26% was observed in patients treated in first relapse only¹⁴. In general, the standard of care for treatment of relapsed or refractory (R/R) acute myeloid leukemias with or without an NPM1 mutation is intensive cytotoxic chemotherapy followed by allogeneic hematopoietic stem cell transplantation⁷. However, this intensive treatment plan is generally reserved for younger patients or older patients with high functional status, both of whom are likely to tolerate such treatment without significant treatment-related complications. Since the median age at initial AML diagnosis is 69, most patients that develop AML are not optimal candidates for intensive treatment with transplant due to age or the common comorbid diseases that increase in occurrence with age⁸. As mentioned above, although in frontline disease

⁷ NCCN Guidelines Version 2.2024 Acute Myeloid Leukemia (Age≥18 years), page AML-8, Accessed 4/1/2024, https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

⁸ Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER AML Stat Database: Incidence - SEER Research Data, SEER 22 2016–2020, All Races, Both Sexes National Cancer Institute, DCCPS, Surveillance Research Program, released April 2023, based on the November 2022 submission.

NPM1 mutation can confer an improved prognosis, in the R/R setting median survival for NPM1 mutant acute myeloid leukemia is less than 1 year (6.1 months), and 5-year OS is less than 10%. There are no prospective trials for treatment of R/R NPM1-m acute leukemia. CR rates for patients treated with salvage chemotherapy depend on age, number of prior relapses, and refractoriness to last line of therapy. In a retrospective analysis of 206 adult patients with NPM1-m AML treated at MD Anderson Cancer Center between September 2012 and December 2020, Issa, et al., reported a 24% CR rate for all lines of therapy with a 32% CR rate with the first salvage therapy after relapse, 14% CR rate after the second salvage, therapy and 7% after a third or later salvage therapy⁹.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation¹⁰.

SNDX-5613 (revumenib) is another Menin inhibitor that was granted BTDR on 11/30/2022 for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia harboring a KMT2A rearrangement. The development programs for reveumenib and ziftomenib have diverged despite both being Menin inhibitors. The sponsors of revumenib have focused their clinical studies primarily on KMT2A-rearranged leukemia, whereas ziftomenib has focused on NPM1-m AML. Therefore, if BTDR is granted for this second Menin inhibitor, it will be for a different indication than was granted for revumenib.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR

The BTDR is based on the preliminary results from study KO-MEN-001 “A Phase 1/2 First in Human Study of the Menin-MLL (KMT2A) Inhibitor KO-539 in Patients with Relapsed or Refractory Acute Myeloid Leukemia” (Table 1). Response by line of treatment is shown in Table 2 below.

Study KO-MEN-001 is ongoing. Only the Phase 1b cohort of patients with NPM1-m AML has final response assessment data, while the results for the Phase 2 patients are as of a data cutoff of January 5, 2024. The sample size numbers include all patients enrolled to the various cohorts as of the data cutoff date. The efficacy data includes patients with NPM1-m AML treated at the RP2D of 600 mg daily from the Phase 1b cohort (N=20) and patients who were evaluable for efficacy from the Phase 2 cohort (N=46). The safety analysis is for all patients with NPM1-m AML treated at the RP2D dose (Phase 1b N=20, Phase 2 N=50).

Table 1: Study KO-MEN-001

DESIGN	
Design	Open-label, single-arm, dose-escalation/dose-expansion first-in-human study of Ziftomenib as monotherapy
Eligible population	Adult patients with R/R AML, defined as those who have failed or are not appropriate for any approved standard-of-care (SOC) therapies, or hematopoietic stem cell transplant (HSCT) Phase 1b: Adult R/R AML patients that have a documented KMT2A-r or, Phase 1b and Phase 2: Adult R/R AML patients that have a documented NPM1-m.
Treatment schedule	Oral ziftomenib (capsule) once daily in 28-day cycles until progression or unacceptable toxicity
Cohorts	Phase 1 Part 1a: Any R/R AML Phase 1 Part 1b: R/R AML with either KMT2A-R or NPM1-m Phase 2: R/R AML with NPM1-m
Sample size	Phase 1 Part 1a: 30 patients with R/R AML Phase 1 Part 1b: 53 patients with NPM1-m and KMT2A-r R/R AML

⁹ Issa GC, Bidikian A, Venugopal S, et al. Clinical outcomes associated with NPM1 mutations in patients with relapsed or refractory AML. Blood Adv. 2023;7(6):933-942. doi:10.1182/bloodadvances.2022008316

¹⁰ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

	Phase 2: up to 85 patients with NPM1-m AML		
Primary efficacy endpoint	CR+CRh		
Efficacy analysis plan	A single proportion binomial test with at least 89% power and 1-sided significance level of 2.5% to exclude CR+CRh rate of 12%.		
SUBJECTS			
Number of subjects enrolled	Overall enrollment to data cut date (January 5,2024) Phase 1 Part 1a: 30 patients with AML Phase 1 Part 1b: 53 patients with NPM1-m and KMT2A-r AML Phase 2: 50 of a planned 85 NPM1-m AML NPM1-m AML treated at RP2D: 20 in Phase 1b, 50 in Phase 2		
Subject characteristics	Demographics	Disease characteristics	
	Median age: 70 (range, 22-86) Male/Female: 44% / 56% Race: White 78.6% Black 1.4% Asian 4.3% Chose not to respond 14.3% Other 1.4%	Median prior therapies: 2 (range, 1-10) Prior HSCT: 18.6% Prior Venetoclax Exposure: 57% Co-Mutations: FLT3 23% IDH1/2 19%	
RESULTS			
Phase	Phase 1b: 600 mg (n=20) Aug 30, 2023	Phase 2 (N=46) Jan 5, 2024	Phase 1b & 2 (N=66) Jan 5, 2024
CR rate (95% CI)	7/20 (35%) [15.4,59.2]	5/46 (11%) [3.6,23.6]	12/66 (18%) [9.8,29.6]
CR+CRh rate (95% CI)	7/20 (35%) [15.4,59.2]	9/46 (19.6%) [9.4,33.9]	16/66 (24.2%) [14.5,36.4]
DOR (CR/CRh) Median (95% CI)			5.6 months (1,8.2) With median follow up of 7.5 months

The CR+CRh rate of 24.2% with a CI excluding rates less than 14%, in addition to the median duration of response being 5.6 months, was considered preliminary evidence of activity of ziftomenib for the treatment of R/R NPM1-m AML.

- b. Include any additional relevant information.

Table 2: Response analysis by line of treatment

Best Overall Response, n (%) [95% CI]	Phase 1b: 600 mg QD (N=20) Aug 30, 2023	Phase 2 (N=46) Jan 5, 2024	Phase 1b & 2 (N=66) Jan 5, 2024
CR – Overall	7 (35.0) [15.4, 59.2]	5 (10.9) [3.6, 23.6]	12 (18.2) [9.8, 29.6]
2 nd line	n=4 3 (75.0%) [19.4, 99.4]	n=17 4 (23.5%) [6.8, 49.9]	n=21 7 (33.3%) [14.6, 57.0]

3 rd line +	n=16 4 (25.0%) [7.3, 52.4]	n=29 1 (3.4%) [0.1, 17.8]	n=45 5 (11.1%) [3.7, 24.1]
CR/CRh – Overall	7 (35.0) [15.4, 59.2]	9 (19.6) [9.4, 33.9]	16 (24.2) [14.5, 36.4]
2 nd line	n=4 3 (75.0) [19.4, 99.4]	n=17 5 (29.4) [10.3, 56.0]	n=21 8 (38.1) [18.1, 61.6]
3 rd line +	n=16 4 (25.0) [7.3, 52.4]	n=29 4 (13.8) [3.9, 31.7]	n=45 8 (17.8) [8.0, 32.1]

The data from the Phase 1b portion of the study show that the kinetics of response to ziftomenib are different from that of cytotoxic chemotherapy. This was seen in the time to response data that showed median time to response in the Phase 1b cohort was 51 days (2 cycles) and median time to CR of 70 days (3 cycles). Should this median time to response be consistent in the Phase 2 portion of the study, the CR/CRh rates would be anticipated to improve with additional follow-up.

Additional insight from the Phase 1b cohort included favorable responses in patients with targetable co-mutations whose disease had failed to respond to prior targeted therapy for these mutations:

- 2/6 (33%) CR with FLT3 co-mutations
- 4/8 (50%) CR with IDH co-mutations
- 2/4 (50%) CR with both co-mutations

Venetoclax is approved in combination with either a hypomethylating agent (HMA) (azacitidine or decitabine) or low dose cytarabine (LDAC) for the treatment of newly diagnosed AML in adult patients over 75 or those who have comorbidities that preclude use of intensive chemotherapy. These venetoclax combinations are also used for off-label in patients with R/R AML without prior venetoclax treatment. Interestingly, patients that are R/R after venetoclax tend to have poor response to later lines of therapy and short overall survival¹¹. However, patients treated with ziftomenib after venetoclax treatment had preserved CR/CRh rates of 21.6%, suggesting orthogonality to prior venetoclax treatment (Table 3).

Table 3: Response based on prior venetoclax exposure.

Best Overall Response n (%) [95% CI]	Received Venetoclax Prior to KO-MEN-001 Phase 1b & Phase 2 (N=37)	Venetoclax Naïve Prior to KO- MEN-001 Phase 1b & Phase 2 (N=29)
CR – Overall	5 (13.5%) [4.5, 28.8]	7 (24.1%) [10.3, 43.5]
2 nd line	n=8 3 (37.5%) [8.5, 75.5]	n=13 4 (30.7%) [9.1, 61.4]
3 rd line +	n=29 2 (6.9%) [0.8, 22.8]	n=16 3 (18.7%) [4.0, 45.6]
CR/CRh – Overall	8 (21.6%) [9.8, 38.2]	8 (27.6%) [12.7, 47.2]
	n=8	n=13

¹¹ Maiti A, Rausch CR, Cortes JE, et al. Outcomes of relapsed or refractory acute myeloid leukemia after frontline hypomethylating agent and venetoclax regimens. *Haematologica*. 2021;106(3):894-898. Published 2021 Mar 1. doi:10.3324/haematol.2020.252569

2 nd line	3 (37.5%) [8.5, 75.5]	5 (38.4%) [13.9, 68.4]
3 rd line +	n=29 5 (17.2%) [5.8, 35.8]	n=16 3 (18.7%) [4.0, 45.6]

Comparison to Available Therapy

The current standard of care for treatment of R/R NPM1-m AML is conventional cytotoxic chemotherapy. There are no clinical trials of conventional therapy for treatment of R/R NPM1-m AML specifically. Additionally, the few trials of chemotherapy for R/R AML that provide retrospective outcomes by specific mutation do not allow for a single reliable estimate of response for the subpopulation. Therefore, the Division chose to use a combination of the retrospective analysis published by Issa, et al., and the analysis of the control arm of the Phase 3 ADMIRAL trial for FLT3 mutated R/R AML, in which 47% of the patients had co-occurring NPM1 mutations, to establish an efficacy benchmark^{9,12}. It should be noted that while the population in the ADMIRAL study is confounded by co-occurring FLT3 mutations. The Division found these results to be relevant due to the common co-occurrence of these two mutations in AML patients.

Since ziftomenib is not a myelosuppressive drug, the Division could use CR+CRh as the endpoint to assess its clinical activity as a palliative agent. For such drugs, achievement of CR or CRh has been associated with transfusion independence and reduced risks of infection and bleeding while on active treatment. Given that treatment with cytotoxic chemotherapy induces the need for transfusions and increases the risks of infection and bleeding, the palliative benefit of the CRh component of the endpoint would not apply to cytotoxic chemotherapy, so CR is used as the measure of benefit needed to outweigh the toxicities instead. The differences between the applicable endpoints complicate comparisons.

Issa, et al., noted difference in response by lines of therapy, with later lines of therapy being less effective for both NPM1-m and NPM1 wt patients. Moreover, Issa, et al., differentiated the results by intensity of treatment into high or low intensity treatment. As ziftomenib is unlikely to be used in patients eligible to receive intensive reinduction therapy, the Division felt that comparison of the ziftomenib results to the lower intensity treatment from this retrospective analysis would be appropriate for these patients. For patients treated with ziftomenib, the 95% CI for CR (9.8-29.6%) excluded the CR rate with lower intensity salvage chemotherapy (6%) (Table 4**Error! Reference source not found.**). For the patients treated with ziftomenib as second line therapy, the point estimate and 95% CI for CR with ziftomenib (33.3% (14.6-57.0)) exceeded the CR rate observed for lower intensity salvage chemotherapy (10%). For patients treated with ziftomenib as a third or later line of therapy, the point estimate and 95% CI for CR with ziftomenib (11.1% (3.7-24.1)) exceed the point estimate for lower intensity salvage chemotherapy in this line (5%) but did not exclude it due to the wide confidence interval. Moreover, the results from Smith, et al., showed that in a multicenter randomized trial, patients with R/R NPM1-m/FLT3-m AML had a CR/CRh rate of 12.1% on the chemotherapy control arm¹². When comparing this CR/CRh rate to that observed in KO-MEN-001 of 24.2 % (14.5- 36.4), ziftomenib excluded the CR/CRh rate of 12.1%. The Division concluded that the results with ziftomenib showed preliminary evidence of substantial improvement in CR/CRh compared to available lower intensity salvage therapy for these patients. However, the Division acknowledges that the CR rates would be lower than higher intensity therapy (up to 58% in Issa, et al⁹), and include both data from the FDA review of gemtuzumab and published data in the last two columns of Table 4, below. As such, we also paid careful attention to safety data in our assessment of substantial improvement over available therapy.

¹² Smith CC, Levis MJ, Perl AE, et al. Molecular profile of FLT3-mutated relapsed/refractory patients with AML in the phase 3 ADMIRAL study of gilteritinib. Blood Adv. 2022;6(7):2144-2155. Blood Adv. 2022;6(22):5886. doi:10.1182/bloodadvances.2022009077

Table 4: Response comparison to available therapy.

Best Overall Response, n (%) [95% CI]	Ziftomenib Phase 1b & 2 Jan 5, 2024 (N=66)	All Chemotherapy for NPM1-m AML (Issa et al)⁹(N=206)	Less intensive Chemotherapy for NPM1-m AML (Issa et al)⁹(N=109)	ADMIRAL all FLT3 ITD patients on chemotherapy^{12,13} (N= 124)	Gemtuzumab ozogamicin R/R AML (First relapse only)¹⁴ (N=57)	Investigators choice R/R AML (Roboz et al)¹⁵ (N=190)
CR – Overall	12 (18.2) [9.8, 29.6]	24	7 (6)	10.5	26 (16-40)	12
2 nd line	n=21 7 (33.3%) [14.6, 57.0]	N=132 42 (32)	n=63 6 (10)	NR	26 (16-40)	NR
3 rd line +	n=45 5 (11.1%) [3.7, 24.1]	N=168 18(10.7)	N=100 5 (5%)	NR	NR	NR
CR/CRh – Overall	16 (24.2) [14.5, 36.4]	NR	NR	15.3 (12.1) [#]	NR	NR

#NPM1-m patients on chemotherapy arm¹²

Safety Data

The sponsor did not comment on fatal adverse events, but the Division is aware of fatal cases of differentiation syndrome (DS) on Study KO-MEN-001 that occurred during the dose escalation phase of the trial. This led to the study being placed on partial clinical hold for a time until more robust monitoring and treatment of differentiation syndrome were instituted. An analysis of which patients had experienced the fatal and high-grade DS events identified patients with KMT2A-r AML as having a higher risk for more severe differentiation syndrome with ziftomenib treatment than patients with NPM1-m AML. This safety finding led the sponsor to focus their monotherapy development exclusively on patients with NPM1-m AML with plans to investigate KMT2A-r AML in future combination therapy trials.

Treatment emergent adverse events for NPM1-m AML patients treated at the RP2D are presented in Table 5. All-grade adverse events (AEs) occurring in > 25% of enrolled patients were thrombocytopenia, diarrhea, anemia, and DS. Grades 3-5 AEs occurring in >5% of patients were thrombocytopenia, febrile neutropenia, DS, neutropenia, asthenia/fatigue, diarrhea, hypokalemia, and pyrexia.

Table 5: Treatment emergent adverse events occurring in ≥ 10% of patients

Preferred Term	All Grade (n=70) n (%)	Grade ≥ 3 (n=70) n (%)
Patients with TEAE	68 (97.1)	30 (42.9)
Thrombocytopenia	20 (28.6)	20 (28.6)
Diarrhoea	19 (27.1)	4 (5.7)

¹³ Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML [published correction appears in N Engl J Med. 2022 May 12;386(19):1868]. N Engl J Med. 2019;381(18):1728-1740. doi:10.1056/NEJMoa1902688

¹⁴ Norsworthy KJ, Ko CW, Lee JE, et al. FDA Approval Summary: Mylotarg for Treatment of Patients with Relapsed or Refractory CD33-Positive Acute Myeloid Leukemia. Oncologist. 2018;23(9):1103-1108. doi:10.1634/theoncologist.2017-0604

¹⁵ Roboz GJ, Rosenblat T, Arellano M, et al. International randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia. J Clin Oncol. 2014;32(18):1919-1926. doi:10.1200/JCO.2013.52.8562

Anaemia	18 (25.7)	2 (2.9)
Differentiation syndrome	18 (25.7)	9 (12.9)
Febrile neutropenia	16 (22.9)	16 (22.9)
Nausea	16 (22.9)	1 (1.4)
Neutropenia	14 (20.0)	5 (7.1)
Hypokalaemia	13 (18.6)	4 (5.7)
Pruritus	13 (18.6)	0 (0)
Constipation	12 (17.1)	1 (1.4)
Oedema peripheral	11 (15.7)	0 (0)
Pyrexia	11 (15.7)	4 (5.7)
Back pain	9 (12.9)	NR
Fatigue	9 (12.9)	4 (5.7)
Pneumonia	9 (12.9)	7 (10)
Asthenia	8 (11.4)	4 (5.7)
Decreased appetite	8 (11.4)	0 (0)
Dyspnoea	8 (11.4)	0 (0)
Hypotension	8 (11.4)	NR
Leukocytosis	8 (11.4)	NR
Weight decreased	8 (11.4)	NR
Abdominal pain (incl lower and upper)	7 (10.0)	1 (1.4)
Alanine aminotransferase increased	7 (10.0)	NR
Aspartate aminotransferase increased	7 (10.0)	NR
Epistaxis	7 (10.0)	NR
Fall	7 (10.0)	NR
Hyperglycaemia	7 (10.0)	NR
Hyponatraemia	7 (10.0)	NR
Vomiting	7 (10.0)	0 (0)

NR-not reported.

We also wished to compare ziftomenib not only to reported data from clinical trials, but also to therapies that are commonly used in the relapsed/refractory disease space (Table 6). As such, we are including safety data from the VIALE-A study, which randomized patients to either venetoclax + hypomethylating agent or placebo + hypomethylating agent. We acknowledge that this study was in the newly diagnosed setting but feel that the safety profile is similar across lines of therapy. In addition, we continue to use data from the ADMIRAL study and the MyloFrance 1 study to compare ziftomenib to other chemotherapeutic regimens in relapsed/refractory AML. Ziftomenib appeared to be less toxic than both lower and higher intensity chemotherapy commonly used for salvage treatments as demonstrated in

Table 6**Error! Reference source not found.**¹⁶. Lower rates of cytopenias, infectious complications, and GI disorders were observed with ziftomenib treatment as compared to both lower and higher intensity salvage regimens.

Table 6: Comparison of select Adverse Events between alternative treatments for AML and ziftomenib

Adverse Event	Ziftomenib 600 mg QD (N=70)	Venetoclax + Aza (N=283) ¹⁶	Placebo + Aza (N=144)	#High Intensity chemo ADMIRAL ¹³	#Low Intensity chemo ADMIRAL ¹³	Gemtuzumab ozogamicin ¹⁴ (N=57)
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https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208573s02/1b1.pdf. Revised June 2022. Accessed April 1, 2024

				(N=68)	(N=41)	
	All Grade % (Grade 3/4 %)	All Grade % (Grade 3/4 %)	All Grade % (Grade 3/4 %)	All Grade % (Grade 3/4 %)	All Grade % (Grade 3/4 %)	All Grade % (Grade 3/4 %)
Gastrointestinal disorders						
Nausea	23 (1)	44 (2)	35 (<1)	38 (0)	17 (0)	71 (0)
Diarrhea	27 (6)	43 (5)	33 (3)	42.6 (4.4)	4.9 (0)	34 (2)
Vomiting	10 (0)	30 (2)	23 (<1)	13.2 (0)	4.9 (0)	61 (0)
Stomatitis	6 (NR)	18 (1)	13 (0)	44 (7)	17 (2)	21 (4)
Abdominal pain	10 (1)	18 (<1)	13 (0)	24 (0)	9.8 (0)	17 (NR)
Blood and lymphatic system disorders						
Neutrophils decreased	23 (23)	98 (98)	88 (81)	52 (48)	51 (46)	NR (NR)
Platelet decreased	29 (29)	94 (88)	94 (80)	73 (73)	69 (62)	NR (NR)
Hemoglobin decreased	26 (3)	61 (57)	56 (52)	59 (41)	46 (26)	NR (NR)
Myelosuppression	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	90 (90)
Febrile Neutropenia	23 (23)	42 (42)	19 (19)	44 (44)	12 (12)	NR (NR)
Infections and infestations						
Pneumonia	13 (10)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	14 (7)
Sepsis	9 (NR)	22 (22)	16 (14)	NR (NR)	NR (NR)	42 (32)
Urinary tract infection	4 (4)	16 (6)	9 (6)	NR (NR)	NR (NR)	NR (NR)

#ADMIRAL events reported for only first 30 days of treatment.

The rate of DS is the major adverse event of special interest for ziftomenib, which does not generally occur during treatment with standard chemotherapy. However, this is an AE that is seen with multiple targeted therapies that release blocks to AML differentiation. The rate and grade of the differentiation syndrome reported here is in line with other FDA-approved medications (ivosidenib, enasidenib, and vesanoid) used in a similar patient population. Therefore, the Division feels that the observed safety advantage of ziftomenib over alternative treatment options for R/R NPM1-m AML, in combination with the efficacy findings, conveys a substantial improvement compared to available therapies.

12. Division's recommendation and rationale (pre-MPC review:

☒ GRANT:

DHM1 recommends that ziftomenib monotherapy be granted Breakthrough Therapy Designation for the treatment of relapsed and refractory NPM1-m AML. There is currently no approved targeted therapy for NPM1-m acute myeloid leukemia; available lower intensity cytotoxic chemotherapy results in low remission rates, particularly in later lines of therapy, with overall survival of less than 6 months. The results of Study KO-MEN-001, with a CR+CRh rate of 24% (with the 95% CI excluding rates less than 14%), in addition to the median duration of responses being 5.6 months, are preliminary clinical evidence of a substantial improvement in efficacy over available therapy. Additionally, the safety profile of ziftomenib is favorable in comparison to that expected for this population when treated with available therapy, providing preliminary clinical evidence of a substantial improvement in safety over available therapy as well. The adverse event of special interest of ziftomenib was differentiation syndrome and could be managed with dose interruption and/or dose reduction. Lastly, ziftomenib administration, given once daily by mouth, would be a less burdensome treatment option for NPM1-m R/R AML since other chemotherapy regimens shown as options above would include an intravenous or intramuscular drug administration given in a healthcare setting⁷.

☐ DENY:

Provide brief summary of rationale for denial:

13. Division's next steps and sponsor's plan for future development:

- a. **If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):**

The sponsor proposes to use the results of the single-arm trial to support a marketing application. They expect the top-line results in Quarter 4 of 2024, with anticipated submission of the NDA in Quarter 1 of 2025. The current study incorporates assessments of QTc effects and drug-drug interactions.

Since receipt of the IND in 2019, the Division has provided advice to the sponsor in 6 formal meetings, teleconferences, or Written Responses Only. The Division will continue to encourage the sponsor to pursue studies of combination regimens in order to maximize the potential of ziftomenib.

- b. **If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:**

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Revised 2-26-2024 /M. Raggio

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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04/18/2024 10:49:18 AM

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