NDA 220305

NDA APPROVAL

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

Dear Matthew Kelly:

Please refer to your new drug application (NDA) received March 31, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for KOMZIFTI (ziftomenib) capsules.

This NDA provides for the use of KOMZIFTI (ziftomenib) capsules for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible nucleophosmin 1 (*NPM1*) mutation who have no satisfactory alternative treatment options.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on September 15, 2025, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 220305**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for KOMZIFTI (ziftomenib) capsules shall be 30 months from the date of manufacture when stored at USP controlled room temperature 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C and 30°C (59°F to 86°F).

ADVISORY COMMITTEE

Your application for KOMZIFTI was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug of this class or in the intended population.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages <1 month of age because necessary studies are impossible or highly impracticable. This is because relapsed or refractory AML is extremely rare in patients aged <1 month of age.

We are deferring submission of your pediatric study for ages 1 month to <17 years of age for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA is a required postmarketing study. The status of this

postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. This required study is listed below.

4929-1 Conduct a molecularly targeted pediatric cancer investigation using age-appropriate pediatric formulations to evaluate dosing, pharmacokinetics, safety, and preliminary efficacy of ziftomenib in combination with fludarabine and cytarabine, in pediatric patients ≥1 month to <17 years of age with relapsed/refractory *KMT2A-r/NUP98-r/NPM1*-m acute leukemia.

Study Completion: 06/2029
Final Report Submission: 02/2030

Submit the protocols to your IND 142028, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of recurrent differentiation syndrome, serious hepatoxicity, and increased risk of cardiac deaths; to identify an unexpected serious risk of increased drug toxicity in patients with severe hepatic impairment and patients with severe renal impairment; and to identify an unexpected serious risk of increased drug toxicity when ziftomenib is coadministered with strong CYP3A or P-gp inhibitors, BCRP inhibitors, and sensitive CYP3A substrates.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

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

4929-2 Conduct a clinical trial to assess and further characterize the known and potential serious risks related to the use of ziftomenib, including whether long-term use of ziftomenib is associated with an increased risk of recurrent differentiation syndrome, serious hepatotoxicity, and increased risk of cardiac deaths. Summarize the safety outcomes when all patients have completed at least three years of treatment with ziftomenib or withdrew earlier.

The timetable you submitted on October 30, 2025, states that you will conduct this trial according to the following schedule:

Trial Completion: 11/2031
Final Report Submission: 05/2032

4929-3 Conduct a clinical pharmacokinetic trial to assess the magnitude of change in exposure of ziftomenib and evaluate a serious potential risk of increased drug toxicity, and to determine an appropriate dosage of ziftomenib to minimize toxicity, in patients with severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

The timetable you submitted on October 30, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 05/2026
Final Protocol Submission: 11/2026
Trial Completion: 11/2029
Final Report Submission: 05/2030

4929-4 Conduct a clinical pharmacokinetic trial to assess the magnitude of change in exposure of ziftomenib and evaluate a serious potential risk of increased drug toxicity, and to determine an appropriate dosage of ziftomenib to minimize toxicity, in patients with severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal

Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on October 30, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 05/2026
Final Protocol Submission: 11/2026
Trial Completion: 11/2029
Final Report Submission: 05/2030

4929-5 Complete KO-MEN-001 Sub-study 2, a clinical pharmacokinetic trial to evaluate the effect of repeat doses of itraconazole on the single dose pharmacokinetics of ziftomenib to assess the serious potential risk of excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled M12 Drug Interaction Studies.

The timetable you submitted on October 30, 2025, states that you will conduct this trial according to the following schedule:

Trial Completion: 06/2027
Final Report Submission: 12/2027

4929-6 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of BCRP inhibitors on the single dose pharmacokinetics of ziftomenib to assess the serious potential risk of excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled M12 Drug Interaction Studies.

The timetable you submitted on October 30, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 05/2026
Final Protocol Submission: 11/2026
Trial Completion: 11/2029
Final Report Submission: 05/2030

4929-7 Complete KO-MEN-001 Sub-study 1, a clinical pharmacokinetic trial to evaluate the effect of repeat doses of ziftomenib on the single dose pharmacokinetics of midazolam to assess the serious potential risk of

excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled M12 Drug Interaction Studies.

The timetable you submitted on October 30, 2025, states that you will conduct this trial according to the following schedule:

Trial Completion:	12/2026
Final Report Submission:	06/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 142028 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o) , REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4929-8 Conduct a study to support the availability of an in vitro diagnostic device (companion diagnostic) for identifying susceptible NPM1 mutations in patients with acute myeloid leukemia for the safe and effective use of ziftomenib.

The timetable you submitted on October 30, 2025, states that you will conduct this study according to the following schedule:

Study Completion:	09/2026
Final Report Submission:	03/2027

4929-9 Conduct an in vitro study to clarify the activity of ziftomenib in acute myeloid leukemia cells with NPM1 mutations other than the A, B, and D subtypes.

The timetable you submitted on October 30, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2026
Final Protocol Submission:	09/2026
Study Completion:	06/2027
Final Report Submission:	12/2027

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

Submit clinical protocols to your IND 142028 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[7].

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[7] https://www.uspnf.com/

If you have any questions, contact Amy Baird, Chief, Project Management Staff, at 301-796-4969 or via e-mail to amy.baird@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Deputy Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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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