CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220305Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	September 22, 2025
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 220305
Product Name, Dosage Form, and Strength:	Komzifti (ziftomenib) capsules, 200 mg
Applicant Name:	Kura Oncology, Inc.
FDA Received Date:	September 15, 2025
TTT ID #:	2025-14062-2
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Kura Oncology, Inc. submitted a revised container label received on September 15, 2025 for Komzifti. We reviewed the revised container label for Komzifti (Appendix A) to determine if it is acceptable from a medication error perspective. The revised label was submitted due to the relocation of Kura Oncology, Inc. Headquarters, which changed the zip code on the container label.

2 CONCLUSION

The container label is acceptable from a medication error perspective, and we have no additional recommendations at this time.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON SEPTEMBER 15, 2025

Container Label:

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/

JODY K KUNDRESKAS
09/22/2025 07:55:05 AM

NICOLE F IVERSON
09/22/2025 08:28:34 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 220305
Submission Number	SDN 001
Submission Date	3/31/2025
Date Consult Received	6/20/2025
Drug Name	Ziftomenib (Komzifti)
Indication	Treatment of adults with relapsed and/or refractory (R/R) acute myeloidleukemia (AML) - hematologic malignancies
Therapeutic Dose	600 mg once daily (QD)
Clinical Division	Division of Hematologic Malignancies 1 (DHM1)
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the Applicant's document.

This review responds to your consult dated 6/20/2025 regarding the Applicant's QT evaluation report. We reviewed the following materials:

- Previous IRT review dated 10/25/2023 and 05/22/2024 in DARRTS;
- Clinical Study Report for KO-MEN-001 (NDA 220305 / SN 0001; link);
- Cardiac Safety Report for KO-MEN-001 (NDA 220305 / SN 0001; link);
- Datasets for KO-MEN-001 (NDA 220305 / SN 0001; link);
- QT Evaluation Report Checklist (NDA 220305 / SN 0001; link);
- Applicant's proposed label (NDA 220305 / SN 0001; link);
- Investigator's brochure version 10.0 (IND 142028 / SN 0303; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA 220305 / SN 0001; link; page 6 - 9).

1 SUMMARY

Ziftomenib is associated with QTc prolongation (7.7 msec [90% CI: 2.9 to 12.6 msec]) – see Table 1. The QTc prolongation is concentration-dependent. However, there is uncertainty in the magnitude of QTc prolongation at the therapeutic dose of 600 mg once daily (QD) for the following reasons:

1. The Applicant's proposed label permits co-administration with strong CYP3A4 inhibitors (~2-fold increase in Cmax). The Cmax for subjects included in the QTc assessment is therefore likely to be ~50% of the clinical Cmax as only the latest version (V9: September 2024) of KO-MEN-001 permitted concomitant administration with a strong CYP3A4 inhibitor.

2. The sample size for the subset of subjects with intensive ECG/PK collection is limited at each time point after the drug reached steady-state, with only 4-9 subjects at the 600 mg dose and 2-4 subjects at the 800 mg dose.
3. Despite the large sample size for the therapeutic dose when ECG data are combined across the phases (n=98), there remains significant uncertainty in the point estimate as reflected in the wide confidence interval (90% CI 2.9 to 12.6 msec). The variability could be due to ECG quality, hypokalemia, which was frequently reported, or variability in exposure (see first bullet). Ultimately, the cause of the increased variability remains unclear.

There were 12 subjects (9%) treated with 600 mg QD with QTcF > 500 msec and 16 (12%) with ΔQTcF > 60 msec. This includes 10 subjects (8%) with both QTcF > 500 msec and ΔQTcF > 60 msec. The outlier analysis is based on all subjects receiving 600 mg QD in KO-MEN-001 (n=133), which included each of the three phases (Phase 1a: 5; Phase 1b: 36; Phase 2: 92).

We recommend inclusion of a warning for QTc prolongation for ziftomenib because concentration-dependent QTc prolongation was observed and there is potential for further increase in QTc prolongation due to CYP3A4 inhibition and inadvertent administration with food (~4x increase in Cmax). Moreover, in section 6 of the proposed label the Applicant also notes that hypokalemia was observed with administration of ziftomenib, which is a risk factor for QTc prolongation and drug-induced torsade de pointes.

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☒ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• The highest dose in the QTc assessment is the therapeutic dose (600 mg QD).
• Concomitant administration with a strong CYP3A4 inhibitor, permitted per label, leads to ~2x increase in Cmax (section 3.1).
• As most versions of KO-MEN-001 prohibited concomitant administration with strong CYP3A4 inhibitors the Cmax for subjects included in the QTc assessment is assumed to be 50% of the clinical Cmax.
• While the label recommends fasted administration there is a potential for further increase in Cmax (~4x) if inadvertently administered with food.
• Data from the intensive PK portion and single time-point in the overall population suggest potential for concentration-dependent QTc prolongation (sections 3.2.3 and 4.5).
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>QTcF</td><td>600 mg</td><td>Cycle 2 Day 1, 4 hours</td><td>7.7</td><td>(2.9 to 12.6)</td></tr>
</table>
</td></tr>
</table>

In vitro findings **In vivo findings**	• Nonclinical integrated risk assessment was not performed.

2 RECOMMENDATIONS

2.1 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 001 (link). Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

The largest mean increase in QTc interval was 7.7 ms (upper confidence interval = 12.6 ms) after administration of ziftomenib 600 mg once daily in patients (b) (4) The increase in the QTc interval was concentration-dependent. There were (b) (4) subjects (b) (4) with QTcF > 500 ms and an increase in QTc > 60 ms over baseline.

Reviewer's comment: QTc prolongation was observed with ziftomenib, and we propose to describe the findings following the recommendation in the draft labeling guidance for QTc prolongation. We propose that the summary of QTc findings is based on all subjects receiving 600 mg QD in KO-MEN-001.

We also recommend inclusion of a warning for QTc prolongation. If a warning is included, then the information about QTc outliers can be moved to the warning section.

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

Ziftomenib (KO-539; MW 717.88 g/mol), is a small molecule inhibitor of the interaction between the menin nuclear protein and the histone methyl transferase, mixed lineage leukemia (MLL, KMT2A). It is in development for relapsed/refractory acute myeloid leukemia. The proposed clinical dosing regimen is 600 mg QD for oral administration.

IRT has previously reviewed this product. The Applicant initially proposed (b) (4) . IRT did not agree with

this approach because [redacted] (b) (4)

The Applicant submitted a plan to use an alternative QTc assessment with study KO-MEN-001, a phase 1/2 first-in-human, open-label, multiple cohort study of ziftomenib in patients with relapsed/refractory acute myeloid leukemia. IRT agreed with the proposed plan and requested clarification regarding the sample size (05/22/2024). At that time, the phase 1 portion of the study was complete.

The current submission includes the final clinical study report and cardiac safety report for study KO-MEN-001. The Phase 1 portion was conducted in two parts: Part 1a was a dose-escalation study in patients with relapsed/refractory acute myeloid leukemia. Part 1b was a dose-validation/cohort expansion in patients with Lysins[K]-specific methyltransferase 2 rearranged (KMT2A-r) or nucleophosmin 1 mutation (NPM1-m) relapsed/refractory acute myeloid leukemia. The Phase 2 portion of the study was not included in the Applicant's QTc assessment.

A total of 30 and 53 patients were enrolled in Part 1a and Part 1b of the study, respectively. In Part 1a, doses of 50, 100, 200, 400, 600, 800, and 1000 mg were administered. In Part 1b, doses of 200 and 600 mg were administered as a QD oral dose under fasted conditions in 28-day cycles. The Applicant's QTc assessment included ECG/PK data from a total of 31 patients (Phase 1a: 14/30; Phase 1b: 17/53) with intensive PK collection in the following ziftomenib dose groups:

- 100 mg (n = 1)
- 200 mg (n = 10)
- 400 mg (n = 2)
- 600 mg (n = 11)
- 800 mg (n = 6)
- 1000 mg (n = 1)

Due to the limited sample size at steady-state in the concentration-QTc analysis set, we also considered Phase 2. We used by-time analysis due to limited time-matched PK data. For additional information on our analysis see section 4.2.1.

3.1.1 Clinical Pharmacology

See highlights of clinical pharmacology and cardiac safety (link pages 6-9).

The therapeutic dose of ziftomenib, 600 mg QD, provides mean Cmax,ss of 881 ng/mL (cycle 2 day 1, Tmax = 3.5 hours, absolute oral bioavailability (Fa) is 12.9 %). The drug follows linear kinetics. It has a long half-life of 61.5 hours (about 2.5 days), accumulation ratio of about 5-fold after 28 days of QD dosing. Steady-state plasma concentrations are achieved by 2 weeks following daily dosing.

Ziftomenib is primarily excreted in feces (89.7% of radioactive dose) and trace amounts in urine (0.525% of the radioactive dose) after oral administration to healthy volunteers. The active metabolites are KO-516 and KO-739 both with Tmax's around 3 hours and

according to the Applicant both have been determined to be minor metabolites (% of drug related exposure for KO-516 was 2.72% and for KO-739 it was 9.18%).

PBPK modeling based on clinical data suggests that CYP3A4 contributes 60% to the overall hepatic metabolism of ziftomenib. The remaining hepatic metabolism (40%) is attributed equally to CYP1A2 and CYP2D6 (20% for each isoform).

The PBPK model predicted that itraconazole (a strong CYP3A4 inhibitor), fluvoxamine (a CYP1A2 inhibitor) and bupropion (a CYP2D6 inhibitor) increased ziftomenib steady state Cmax by 2.12-, 1.44- and 1.15-fold, respectively (PBPK report, Table 1).

A high fat meal increased ziftomenib AUC and Cmax by about 4-fold and Tmax was delayed by 2 hours relative to the fasted state (*see Expected High Clinical Exposure Scenario and Labeling viewpoints below*). The Applicant proposes to administer ziftomenib under fasted conditions, specifically 1 hour before meal or 2 hours after meal.

Population PK indicates that age, sex, and race do not affect the pharmacokinetics of ziftomenib. Further this analysis shows no significant effect of mild or moderate hepatic and renal impairment on the pharmacokinetics of ziftomenib (renal elimination is minimal with only 0.525% of the ziftomenib dose recovered).

Table 2 presents the steady state Cmax at the maximum proposed therapeutic dose (administration with a strong CYP3A4 inhibitor).

Table 2. Summary of Dose and Exposure Assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	600 mg QD, oral tablets with strong CYP3A4 inhibitor*	1850 ng/mL ($C_{max,ss}$)
Applicant's High clinical exposure scenario	No high clinical exposure scenario identified.	1850 ng/mL
Highest dose in QT assessment	600 mg QD, oral tablets**	881 ng/mL
C_{max} Ratio	881 / 1850 = 0.47 for clinical**	

* Concomitant administration with strong CYP3A4 inhibitor is permitted per label. Although high fat meal increases ziftomenib Cmax by 4-fold, ziftomenib is recommended to be taken in fasted state. Inadvertent co-administration with food could result in steady state Cmax of 3524 ng/mL. ** The latest version of the protocol for KO-MEN-001 (v9) permits concomitant administration with strong CYP3A4 inhibitors (see e.g., p102; link). As only the latest version (September 2024) permitted concomitant administration we assume that most subjects included in the QTc assessment did not take concomitant strong CYP3A4 inhibitors.

Reviewer's Comment: *The highest dose in QTc prolongation risk assessment covers the anticipated clinical exposure, but not high clinical exposure scenario. Administration with high fat meal is not likely to be a high clinical exposure scenario as the proposed label recommends administering ziftomenib under fasted conditions. However, a 4-fold increase in Cmax of ziftomenib occurs if administered with food, which is in violation of the recommended dosing procedures.*

3.1.2 Nonclinical Safety Pharmacology Assessments

Previously submitted nonclinical safety data was summarized in the IRT reviews dated 10/25/2023 and 05/22/2024.

In vitro hERG assay

The in vitro hERG assay (KO-TOX-0023, link) assessed the potential effects of ziftomenib (KO-539) on the hERG current in the HEK293 cells. The hERG current was assessed at near physiological temperature (35-37 ºC) using a voltage protocol recommended by the FDA (link). A full blocker (0.5 µM E-4031) was added at the end of the experiment to assess the non-hERG currents induced by the protocol. The positive control ondansetron inhibited hERG potassium currents by 25.9% at 0.5 µM and 78.3% a5 5 µM. Solution samples were collected from the outflow of the perfusion apparatus on the day of experiment for drug concentration verification, the measured concentrations were 0.066 µM and 1.62 µM for the nominal concentrations of 0.1 µM and 2 µM, respectively.

Ziftomenib inhibited the hERG currents by 70.8% at 0.066 µM and 95% at 1.62 µM. The IC50 was not determined but is expected to be smaller than 0.066 µM.

Reviewer's Comment: *The hERG assay met the best practice recommendations by ICH S7B Q&As 2.1. The estimated IC50 of ziftomenib on hERG current is ~ 0.0167µM (nH=0.64), which provides a safety margin of 0.65-fold (MW: 717.9 g/mol; PB:99%) using the high clinical exposure (1850 ng/mL, see Table 1). The results suggest that ziftomenib poses a risk for QT prolongation by inhibition of hERG channel at the therapeutic clinical exposures.*

In vitro hERG, Nav1.5 and Cav1.2 assays

The in vitro hERG assay (KO-TOX-0021, link) assessed the potential effects of ziftomenib (KO-539) on the hERG, Nav1.5 and Cav1.2 currents using the automated QPatch platform at room temperature. The drug concentration verification was not confirmed in the assays. The tested concentrations for each assay were 0.5, 3, 10 and 50 µM. The TurboSol analysis indicated that there were precipitation in concentrations of 10 and 50 µM.

Ziftomenib inhibited the hERG, Nav1.5 and Cav1.2 currents with IC50 values of 1.58 µM, 142 µM and 2.8 µM, respectively.

Reviewer's Comment: *The in vitro hERG, Nav1.5 and Cav1.2 assays showed deviations (room temperature; no drug concentration verification and lack of proper positive controls) from the best practice recommendations by ICH S7B Q&As 2.1. The safety margins of ziftomenib on hERG, Nav1.5 and Cav1.2 current are 61-fold (hERG), 5510 - fold (Nav1.5) and 108-fold using the high clinical exposure (1850 ng/mL, see Table 1). The results suggest that ziftomenib may block both hERG and Cav1.2 currents at the clinical exposure.*

"In a GLP complaint CV assessment in conscious radiotelemetrized beagle dogs (KO-TOX-0022 [link]) at 40, 120 and 200 mg/kg ziftomenib dose demonstrated that there were no ziftomenib-related effects on the QRS complex, RR, QT, or QTc interval durations at any ziftomenib dose level evaluated. No changes in ECG waveform

morphology were considered a result of ziftomenib administration at any dose level." - Highlights of clinical pharmacology and cardiac safety (link)

Reviewer's comment: *The CV study had two phases: 1) CV phase with Latin-square design; 2) PK phase with dose-escalating design. The study included 4 male Beagle dogs and three dose levels: 40, 120, and 200 mg/kg.*

Post-dose signs of emesis were observed in animals receiving 120 and 200 mg/kg in both the CV and PK phase. The impact of the emesis was particularly noticeable in the PK data as a Cmax of 922, 1090, and 387 ng/mL were reported for 40, 120, and 200 mg/kg, respectively. Moreover, the Applicant also notes that there was carry over due to a too short washout period (7 days). Consequently, the interpretability of the exposure data from this study is unclear.

There were no changes in QRS, QTc, or HR. However, a dose-dependent increase in PR was observed.

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for ziftomenib was based on exposure-response analysis on the Phase 1 data, please see section 3.2.3 for additional details.

The Applicant had initially planned to use a MMRM model with ΔQTcF as the dependent variable and time, treatment, and time x treatment interaction, and baseline as covariates. The model also included an unstructured covariance matrix for repeated measures within patients. Alternative covariance matrix models could be explored as needed.

The Applicant performed by-time analyses using MMRM by grouping cycles (Cycle 1 and Cycles 2 + 3), while using the compound symmetric covariance matrix for the repeated measures. The changes to the planned analysis were due to convergence problems.

The LS mean change-from-baseline QTcF ranged from -18.9 ms (90% CI: -38.54 to 0.82) (at Cycle 2 Day 1 pre-dose in the 200 mg dose group) to 10.8 ms (at Cycle 1 Day 8 in the 600 mg dose group). In Cycle 2, Day 1, concentrations were substantially higher than in Cycle 1. In the dose groups with the highest plasma concentrations on this day (600 mg), the -2.0 ms (at Cycle 2 Day 1 2 hours post-dose) to -1.7 ms (at Cycle 2 Day 1 4 hours post-dose).

The Applicant used a similar methodology to analyze HR, QRS, and PR. The same model as described for QTcF interval above was used. No significant changes in HR, QRS, and PR were reported.

Reviewer's comment: *The sample size in the analysis population ranged from 4-9 and 2-4 at post-dose time points after reaching steady-state (Cycle 1 Day 15) for 600 and 800 mg QD, respectively. The limited sample size could have contributed to the convergence issues. Therefore, no independent modeling analysis was performed.*

Descriptive statistics were also performed using the automatic ECG measurements for all subjects in Phase 1a, 1b, and 2. Few subjects (n=5) received 600 mg in Phase 1a, and the summary below therefore only includes mean (SD) for Phase 1b and 2 at the time-point

in Cycle 1 and Cycle 2 with the maximum mean value of change from baseline for subjects received 600 mg. The summary is based on Tables 14.3.6.2.2 and 14.3.6.2.3 included in the tables and figures for the CSR (pages 1905-1939).

Interval	Phase 1b		Phase 2	
	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 1 Day 1	Cycle 2 Day 1
ΔQTcF	4.8 (7.8)	8.9 (20.9)	3.2 (14.8)	8.2 (29.2)
ΔPR	3.1 (13.2)	9.6 (16.4)	2.3 (10.6)	3.5 (17.5)
ΔQRS	-1.3 (16.8)	-2.3 (18.6)	0.7 (8)	0.1 (8.3)
ΔHR[1]	-1 (7.3)	-5.2 (13.6)	-1.5 (7.5)	-8.6 (13.3)

[1]Minimum value.

Reviewer's comment: *Reviewer conducted by-time analysis using descriptive analysis. The results of the Applicant's analysis are consistent with our independent analysis. Please see Section 4.2.1 for more details.*

3.2.1.1 Assay Sensitivity

Not applicable – study did not include placebo or a positive control.

3.2.2 Categorical Analysis

There were outliers for QTcF, 2 subjects in Phase 1a in 200 mg group with QTcF >500 msec, 2 subjects in Phase 1b with QTcF >500 msec (1 subject in 200 mg group and 1 subject in 600 mg group) and 3 subjects in Phase 1b with ΔQTcF >60 msec over baseline (2 in 200 mg group and 1 in 600 mg group). In Phase 2, 10 subjects in 600 mg group with QTcF >500 msec and 14 observations with ΔQTcF >60 msec over baseline (Tables 14.3.6.3.1-14.3.6.3.3 – pages 1955 to 1957).

Reviewer's comment: *We observed 9 subjects with QTcF >500 msec compared to the 14 reported by the Applicant. The difference is due to our analysis being based on average measurements, which excluded visits with collection of single ECGs. We also note that the Applicant appears to be missing 1 subject with QTcF >500 msec and ΔQTc > 60 msec in Phase 2 based on the datasets provided.*

Outliers for PR, QRS, and HR were only presented for the subjects included in the cardiac safety report. In this report, There were four subjects with HR outliers (>100 beats/min), including 2 subjects in 200 mg group, 1 subject in 600 mg group, and 1 subject in 800 mg group, respectively; there was one subject with PR (>220 msec and 25% over baseline) in 200 mg group; and there was one subject with QRS (>120 msec and 25% over baseline) in 200 mg group.

Reviewer's comment: *The results of the review's analysis are based on all subjects with available measurements in both Phase 1 and Phase 2, therefore containing more outliers compared to those of the Applicant's analysis. Please see Section 4.4 for more details.*

3.2.3 Exposure-Response Analysis

The relationship between ΔQTcF and ziftomenib and its 2 major metabolites KO-516 and KO-739 were investigated using a linear mixed-effects modeling approach. The full model included ziftomenib, KO-516, and KO-739 as the explanatory variables, centered baseline QTcF (i.e., baseline QTcF for individual patient minus the population mean baseline QTcF for all patients) as an additional covariate, a fixed intercept (i.e., a population mean intercept), and random effects on intercept and slopes per patient.

Seven concentration-QTc models were explored i.e., the full model with all these 3 analytes (ziftomenib, KO-516, and KO-739) and reduced models including models with only 1 analyte and with any 2 analytes. The model selection procedure was undertaken using the Akaike information criterion (AIC). Model E with the parent drug ziftomenib alone was selected as the primary model (AIC value 650.8). AIC values for all models were very similar with a difference of less than 2%. The Applicant preferred the model with the parent drug alone as the primary one.

According to the Applicant, testing of the assumptions of the linear mixed effect C-QTc model revealed that: 1) No drug effect on HR was observed; 2) exploratory plot indicated a linear concentration-QTc relationship and 3) No time delay (hysteresis) between drug concentrations and ΔQTcF.

Based on the Applicant's C-QTc analysis, the estimated population slope of the concentration-QTc relationship was 0.014 msec per ng/mL (90% CI: 0.0073 to 0.0212; p = 0.0010) with a large intercept of -9.21 msec (90% CI: -14.804 to -3.620; p = 0.0096).

The model predicted ΔQTcF values for the 600 mg therapeutic dose group were -6.76 msec (90% CI: -12.16 to -1.36) and 8.25 msec (90% CI: -0.41 to 16.91) at the geometric mean ziftomenib Cmax on Cycle 1 Day 1 (172.1 ng/mL) and Cycle 2 Day 1 (1223.9 ng/mL), respectively.

An effect on ΔQTcF with 90% upper confidence interval exceeding 10 msec is predicted for ziftomenib plasma concentrations exceeding approximately 865 ng/mL and an effect with 90% UCI exceeding 20 msec is predicted for ziftomenib plasma concentrations greater than approximately 1380 ng/mL. The prediction results from other models were similar to those from the selected model (Model E, ziftomenib alone) with 90% upper confidence interval exceeding 10 msec can be expected for ziftomenib, KO-516, and KO-739 plasma concentrations of approximately 865, 105, and 878 ng/mL, respectively, and with 90% upper confidence interval exceeding 20 msec can be expected for ziftomenib, KO-516, and KO-739 plasma concentrations of approximately 1380, 169, and 1480 ng/mL, respectively.

Reviewer's Comment: *Although the Applicant conducted linear mixed effects C-QTc modelling, the ECG collection schedule is sparse and does not support testing the assumption of lack of hysteresis. Without evidence on the lack of delayed QTc prolongation risk, the findings of the C-QTc analysis are inconclusive.*

3.2.4 Safety Analysis

In Study KO-MEN-001, in the part 1a dose-escalation portion of the study (n=30 in modified intent-to-treat population), two subjects died from cardiac adverse events. One subject treated with 1000 mg ziftomenib died from cardiac arrest (subject (b) (6) One subject treated with 200 mg ziftomenib died from arrhythmia (subject (b) (6) A review of the narratives for these two subjects showed that both had significant confounding factors. Both experienced QTcF >500 msec during the study, but not within 2 weeks of their death.

Other adverse events potentially related to QT prolongation occurred in KO-MEN-001. Three subjects experienced cardiac arrest (all fatal), four subjects experienced syncope (non-serious), one subject experienced ventricular tachycardia (non-serious), and one subject experienced death (not otherwise specified). Of these nine subjects, three had QTcF measurements exceeding 500 msec:

- Subject (b) (6) had a QTcF interval of 559 msec on day 1, normal QTcF on day 10, and had fatal cardiac arrest on day 17.
- Subject (b) (6) had QTcF measurements between 514 and 562 msec on day 29 and experienced syncope on day 70. The QTcF measurement closest to the syncope event was 450 msec on day 57.
- Subject (b) (6) had a QTcF interval of 512 msec on day 47, and experienced syncope on day 35. For this subject, day 29 QTcF measurements ranged from 420 to 458 msec, and this was the measurement closest to the syncope event.

In the phase 2 portion of the study (n=92, 600 mg QD dose), 13% of subjects experienced electrocardiogram QT prolonged.

The Applicant wrote:

"A small percentage of NPM1-m patients treated with 600 mg ziftomenib in Phase 1 Part 1b EAS and Phase 2 mITT cohorts exhibited QTcF values exceeding 500 msec (8.9%), and 12.5% of patients experienced QTcF interval changes >60 msec from baseline... Notably, only 3 patients had ziftomenib-related QTcF prolongation, 2 of which were Grade 3. Review of these patients identified that all patients were on multiple concomitant QT prolonging medications, 2 had either hypokalemia or hypocalcemia at the time of the event, and the third patient had a medical history of atrial fibrillation. There were no events of Grade 4 QTcF prolongation/Torsades de Pointes. Further cardiodynamic evaluation results (Report KO-PK-0003, Appendix 16.1.9.2) confirmed that ziftomenib had no clinically relevant effect on QTc or other ECG parameters despite the polypharmacy of this population, inclusive of multiple QTc prolonging medications." – Clinical Study Report page 312 (link)

Reviewer's comment: *Events identified to be of clinical importance per the ICH E14 guidelines occurred in this study. Those that were considered related to ziftomenib by the investigator were of moderate severity. The subjects who experienced adverse events potentially related to QT prolongation either had no QTcF measurements >500 msec or did not have elevated QTcF measurements within 10 days of those events.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| >10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

ECGs were collected on paper. ECGs collected for subjects in the concentration-QTc analysis were subsequently scanned and analyzed using digital calipers. This resulted in automatic ECG measurements, as generated by the recording device, for all subjects and semi-automatically read paper ECGs for subjects included in the concentration-QTc analysis (n=31). Not all ECG time-points included collection of ECGs in triplicate.

There were too few subjects with ECG data at the therapeutic dose or higher with semi-automatic measurements. We therefore focused our analysis on all subjects in Phase 1a, 1b, and 2 with automatic ECG measurements. The analysis population consists of 175 subjects in total: Phase 1a (n=30). Phase 1b (n=53), Phase 2 (n=92). This includes 133 subjects receiving 600 mg with 98 subjects on cycle 2 day 1.

The by-time analysis and the concentration-QTc analysis were carried out in subjects receiving 600 mg only while included all dose groups in the categorical analysis.

There were 2 missing automatic observations in the Phase 1 dataset at scheduled timepoint without reasons provided:

- KO-MEN-001MAIN-(b) (6)200 mg, at Cycle 2 Day 1 hour=2
- KO-MEN-001MAIN-(b) (6) 800 mg, at Cycle 2 Day 1 hour=4

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The reviewer evaluated the ΔQTcF effect using descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for the treatment group of ziftomenib 600 mg. The maximum ΔQTcF values by treatment are shown in Table 3.

Figure 1. Mean and 90% CI of ΔQTcF Time-Course (Unadjusted CIs)

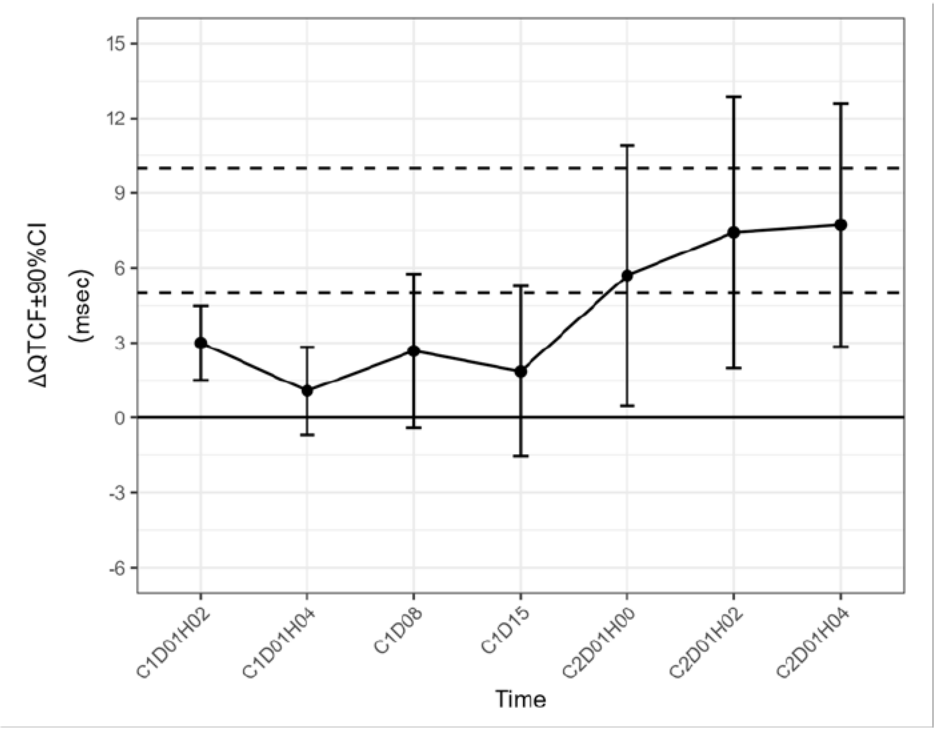


Table 3. Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Actual Treatment	Analysis Visit	N	Time (hour)	ΔQTCF (msec)	90.0% CI (msec)
Ziftomenib 600 mg	C2D01H04	87	4.0	7.7	(2.9 to 12.6)

4.3.1.1 Assay Sensitivity

Not applicable – no positive control was included.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for the treatment group of ziftomenib 600 mg. The minimum ΔHR values by treatment are shown in Table 4. A small mean decrease in HR was observed (mean ΔHR ~7 beats/min).

Figure 2. Mean and 90% CI of ΔHR Time-Course

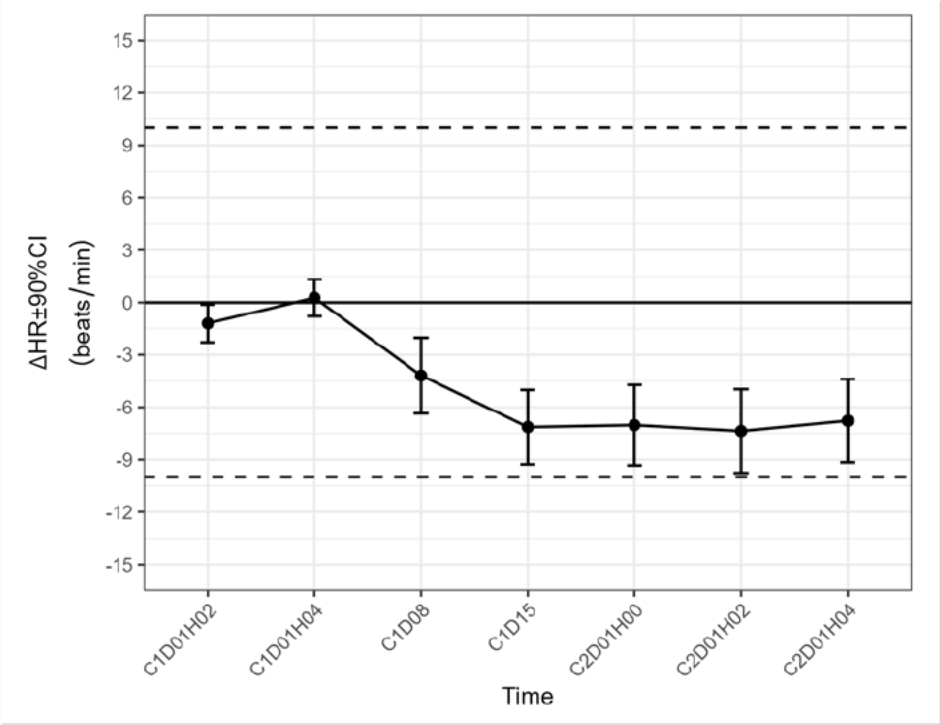


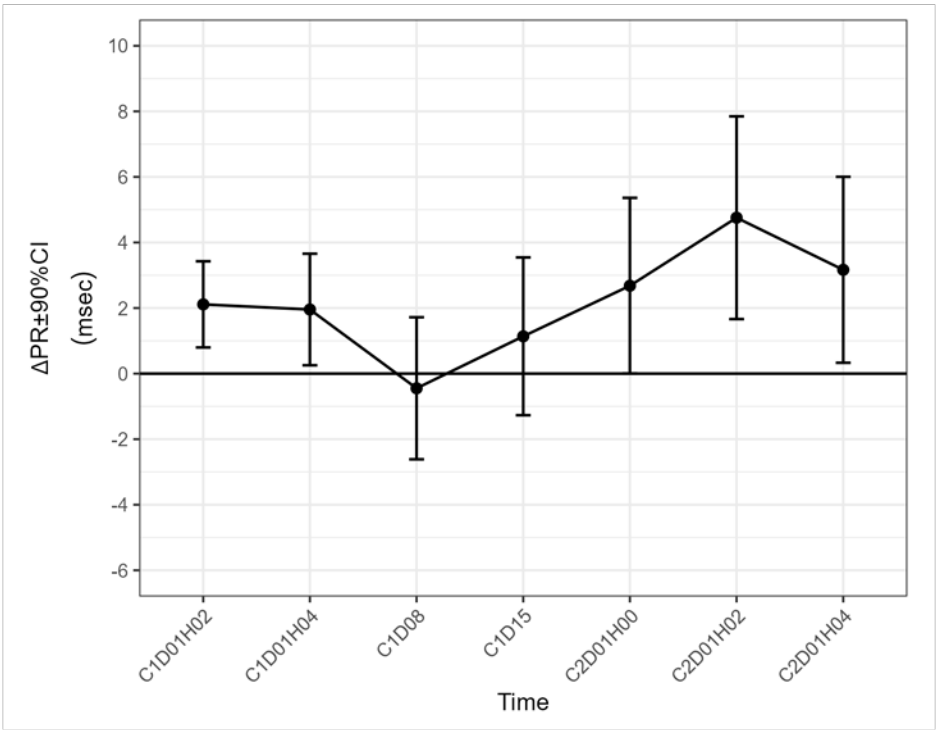
Table 4. Point Estimates and the 90% CIs Corresponding to the Smallest Lower Bounds for ΔHR

Actual Treatment	Analysis Visit	N	Time (hour)	ΔHR (beats/min)	90.0% CI (beats/min)
Ziftomenib 600 mg	C2D01H02	89	2.0	-7.4	(-9.8 to -5.0)

4.3.3 PR

Figure 3 displays the time profile of ΔPR for the treatment group of ziftomenib 600 mg showing no significant increase or decrease in ΔPR.

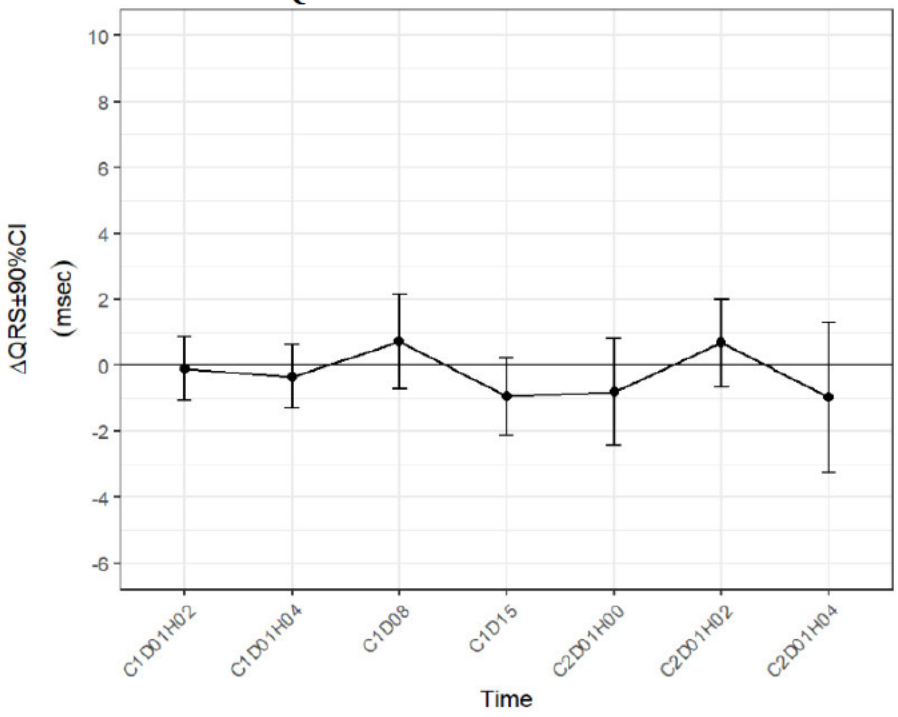
Figure 3. Mean and 90% CI of ΔPR Time-Course



4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for the treatment group of ziftomenib 600 mg showing no changes in ΔQRS.

Figure 4. Mean and 90% CI of ΔQRS Time-Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

Table 5 lists the number of subjects, as well as the number of observations with QTcF values of ≤450 msec, >450 and ≤480 msec, >480 and ≤500 msec, and >500 msec without and without a change from baseline >60 msec. In the ziftomenib 200 mg treatment group, there was 1 subject had observed QTcF above 500 msec and change from baseline >60 msec; there was 1 subject had observed QTcF above 500 msec and change from baseline ≤60 msec. In the ziftomenib 600 mg treatment group, there were 4 subjects had observed QTcF above 500 msec and change from baseline >60 msec; there were 3 subjects had observed QTcF above 500 msec and change from baseline ≤60 msec.

Table 5. Categorical Analysis for QTcF (maximum)

Actual Treatment	Total (N)		Value <=450 msec		450 msec < Value <=480 msec		480 msec < Value <=500 msec		Value >500 msec & <=60 msec		Value >500 msec & >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ziftomenib 200 mg	23	171	10 (43.5%)	132 (77.2%)	8 (34.8%)	33 (19.3%)	3 (13.0%)	4 (2.3%)	1 (4.3%)	1 (0.6%)	1 (4.3%)	1 (0.6%)

Actual Treatment	Total (N)		Value <=450 msec		450 msec < Value <=480 msec		480 msec < Value <=500 msec		Value >500 msec & <=60 msec		Value >500 msec & >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ziftomenib 600 mg	133	910	81 (60.9%)	764 (84.0%)	33 (24.8%)	113 (12.4%)	12 (9.0%)	20 (2.2%)	3 (2.3%)	7 (0.8%)	4 (3.0%)	6 (0.7%)

4.4.2 HR

Table 6 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were 1 subject in the ziftomenib 50 mg treatment group, 8 subjects in the ziftomenib 200 mg treatment group, 3 subjects in the ziftomenib 400 mg treatment group, 33 subjects in the ziftomenib 600 mg treatment group, and 3 subjects in ziftomenib 800 mg treatment group with maximum HR values greater than 100 beats/min.

Table 6. Categorical Analysis for HR (Maximum)

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ziftomenib 50 mg	1	5	0 (0%)	3 (60.0%)	1 (100.0%)	2 (40.0%)
Ziftomenib 200 mg	23	175	15 (65.2%)	152 (86.9%)	8 (34.8%)	23 (13.1%)
Ziftomenib 400 mg	5	33	2 (40.0%)	30 (90.9%)	3 (60.0%)	3 (9.1%)
Ziftomenib 600 mg	133	911	100 (75.2%)	862 (94.6%)	33 (24.8%)	49 (5.4%)
Ziftomenib 800 mg	11	88	8 (72.7%)	83 (94.3%)	3 (27.3%)	5 (5.7%)

4.4.3 PR

Table 7 lists the categorical analysis results for PR (≤220 msec, and >220 msec; with and without 25% increase over baseline). There were 1 subject in the ziftomenib 200 mg treatment group, 1 subject in the ziftomenib 400 mg treatment group, 1 subject in the ziftomenib 600 mg treatment group, and 1 subject in ziftomenib 800 mg treatment group with PR >220 msec with 25% increase over baseline.

Table 7. Categorical Analysis for PR (Maximum)

Actual Treatment	Total (N)		Value <=220 msec		Value >220 msec & <25%		Value >220 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ziftomenib 200 mg	23	175	22 (95.7%)	174 (99.4%)	0 (0%)	0 (0%)	1 (4.3%)	1 (0.6%)

Actual Treatment	Total (N)		Value <=220 msec		Value >220 msec & <25%		Value >220 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ziftomenib 400 mg	4	25	3 (75.0%)	24 (96.0%)	0 (0%)	0 (0%)	1 (25.0%)	1 (4.0%)
Ziftomenib 600 mg	131	889	127 (96.9%)	872 (98.1%)	3 (2.3%)	16 (1.8%)	1 (0.8%)	1 (0.1%)
Ziftomenib 800 mg	11	83	9 (81.8%)	81 (97.6%)	1 (9.1%)	1 (1.2%)	1 (9.1%)	1 (1.2%)

4.4.4 QRS

Table 8 lists the categorical analysis results for QRS (≤120 msec, and >120 msec; with and without 25% increase over baseline). There were 2 subjects in the ziftomenib 200 mg treatment group, 1 subject in the ziftomenib 400 mg treatment group and 1 subject in the ziftomenib 600 mg treatment group observed QRS above 120 msec and >25% increase.

Table 8. Categorical Analysis for QRS

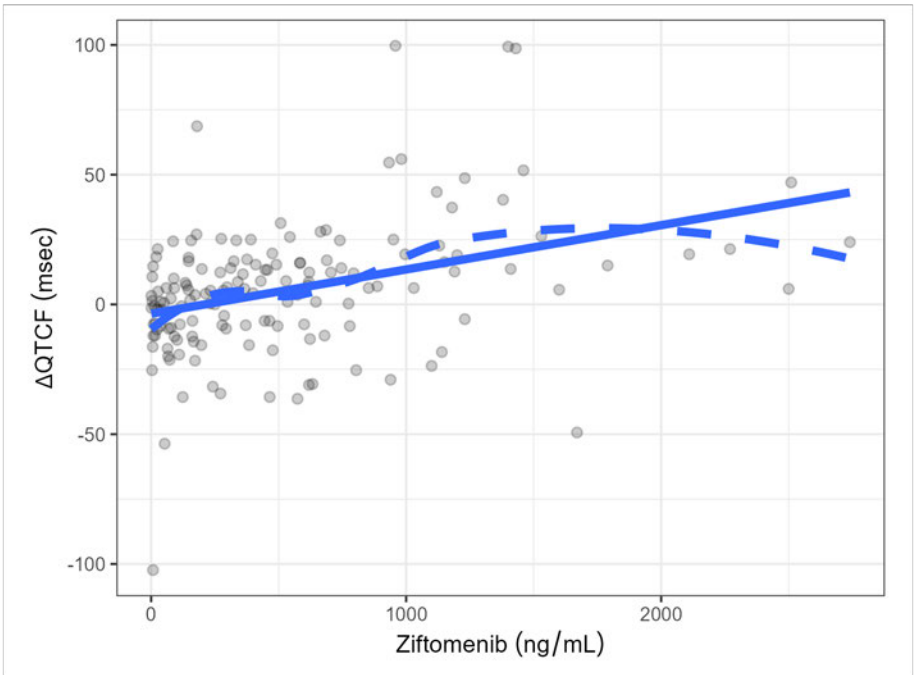
Actual Treatment	Total (N)		Value <=120 msec		Value >120 msec & <25%		Value >120 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ziftomenib 200 mg	23	175	20 (87.0%)	166 (94.9%)	1 (4.3%)	5 (2.9%)	2 (8.7%)	4 (2.3%)
Ziftomenib 400 mg	5	33	4 (80.0%)	32 (97.0%)	0 (0%)	0 (0%)	1 (20.0%)	1 (3.0%)
Ziftomenib 600 mg	133	911	124 (93.2%)	866 (95.1%)	8 (6.0%)	44 (4.8%)	1 (0.8%)	1 (0.1%)

4.5 Exposure-Response Analysis

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK. There were only one time-point with ECG and PK in the full study population, i.e., at pre-dose on day 1 of Cycle (C2D100H), time matched PK/ECG pair was only available this time point. For this reason, it is not possible to test the assumptions of the linear mixed effects C-QTc model as recommended by the scientific white paper.

Nevertheless, a scatter plot of ΔQTcF versus concentration at C2D100H (linearity plot) was constructed to explore potential concentration-QTc relationship. As Figure 5 shows, there is a potential association between ΔQTcF and ziftomenib concentration.

Figure 5. Assessment of Linearity of the Concentration-QTcF Relationship



4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF THE APPLICANT'S CLINICAL QT STUDIES

See previous review dated 05/22/2024.

5.2 EVALUATION OF THE APPLICANT'S CLINICAL QT ANALYSIS PLAN

See previous review dated 05/22/2024.

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/

LARS JOHANNESEN
09/17/2025 11:14:21 AM

RAMAN K BAWEJA
09/17/2025 11:29:54 AM

ELIFORD N KITABI
09/17/2025 11:57:55 AM

WEI LIU
09/17/2025 12:00:30 PM

QIANYU DANG
09/17/2025 01:17:15 PM

YU-TING WENG
09/17/2025 01:24:21 PM

MICHAEL Y LI
09/17/2025 02:26:03 PM

ANNE E BUNNER
09/17/2025 02:42:24 PM

CHRISTINE E GARNETT
09/17/2025 02:43:26 PM

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

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

Memorandum

Date: September 9, 2025

To: Amy Baird, Chief of Project Management Staff, Division of Hematologic Malignancies I (DHM1)

From: Samia Alam, PharmD, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for KOMZIFTI™ (ziftomenib) capsules, for oral use

NDA: 220305

Background:
In response to DHM1's consult request dated April 11, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for KOMZIFTI™ (ziftomenib) capsules, for oral use.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 29, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on September 8, 2025.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on September 5, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Samia Alam at (240) 402-3695 or Samia.Alam@fda.hhs.gov.

Section	Statement from draft	Comment
HIGHLIGHTS **WARNING: DIFFERENTIATION SYNDROME**	**Differentiation syndrome, which can be fatal, has occurred with KOMZIFTI. If differentiation syndrome is suspected, interrupt KOMZIFTI and initiate oral or intravenous corticosteroids with hemodynamic and laboratory monitoring; resume KOMZIFTI upon symptom improvement. (2.5, 5.1, 6.1)**	We note that the approved labeling for another menin inhibitor indicated for relapsed or refractory acute myeloid leukemia (R/R AML), Revuforj, and other products indicated for R/R AML, including Idhifa, Rezlidhia, Tibsovo, and Xospata, all specify to continue corticosteroid therapy and hemodynamic monitoring "until symptom resolution" for differentiation syndrome. For consistency with other labels, we recommend including this information.
HIGHLIGHTS **ADVERSE REACTIONS**	The most common adverse reactions (≥20%) are nausea, fatigue, diarrhea, edema, differentiation syndrome, pruritus, febrile neutropenia, (b) (4). (6.1)	We note that per Table 2 in the FPI, (b) (4) Thus, OPDP recommends removing (b) (4) from this list if this is still the case after the sponsor updates the adverse reactions based on the response to the IR.
HIGHLIGHTS **DRUG INTERACTIONS**	Strong or moderate CYP3A Inhibitors: Monitor more frequently for adverse reactions. Strong or Moderate CYP3A4 Inducers: Avoid concomitant use. (7.1) (b) (4)	For consistency with the statements regarding CYP3A4 inducers (b) (4) and to help guide the reader to additional information on the effect of CYP3A inhibitors on Komzifti, OPDP recommends also including a reference to section 7.1 next to the statement regarding CYP3A inhibitors.
FULL PRESCRIBING INFORMATION: CONTENTS*	**13 NONCLINICAL TOXICOLOGY** 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	We note the current TOC does not include section 13.2 Animal Toxicology and/or Pharmacology that was added to the FPI. OPDP recommends revising the TOC to reflect all proposed updates in the FPI..
FULL PRESCRIBING INFORMATION **WARNING: DIFFERENTIATION SYNDROME**	**Differentiation syndrome, which can be fatal, has occurred with KOMZIFTI. Signs and symptoms may include fever, joint pain, hypotension, hypoxia, dyspnea, rapid weight gain or peripheral edema, pleural or**	We note that the approved labeling for another menin inhibitor indicated for R/R AML, Revuforj, and other products indicated for R/R AML, including Idhifa, Rezlidhia, Tibsovo, and Xospata,

	pericardial effusions, acute kidney injury, and rashes.	all include "pulmonary infiltrates" as a sign or symptom of differentiation syndrome. We defer to DHM1 if this sign or symptom should be included.
FULL PRESCRIBING INFORMATION **WARNING: DIFFERENTIATION SYNDROME**	**If differentiation syndrome is suspected, interrupt KOMZIFTI, and initiate oral or intravenous corticosteroids with hemodynamic and laboratory monitoring; resume KOMZIFTI upon symptom improvement *[see Dosage and Administration (2.5), Warnings and Precautions (5.1), and Adverse Reactions (6.1)].***	We note that the approved labeling for another menin inhibitor indicated for R/R AML, Revuforj, and other products indicated for R/R AML, including Idhifa, Rezlidhia, Tibsovo, and Xospata, all specify to continue corticosteroid therapy and hemodynamic monitoring "until symptom resolution". For consistency with other labels, we recommend including this information.
DOSAGE AND ADMINISTRATION **2.2 Recommended Dosage**	Do not start KOMZIFTI until the WBC is reduced to less than 25 Gi/L.	OPDP recommends defining acronyms (i.e. WBC) at first use.
ADVERSE REACTIONS **6.1 Clinical Trials Experience**	The most common adverse reactions, including laboratory abnormalities (≥20%) were nausea, fatigue, diarrhea, edema, differentiation syndrome, pruritus, febrile neutropenia, (b) (4)	(b) (4) Thus, OPDP recommends removing (b) (4)
ADVERSE REACTIONS **6.1 Clinical Trials Experience**	**Table 1 Adverse Reactions Reported in ≥20% (Any Grade) or ≥5% (Grade 3 or 4) of Patients with Relapsed or Refractory AML in KO-MEN-001**	We note that all grade leukocytosis and grade 3 or 4 leukocytosis is listed in Table 2 to have occurred in 16% and (b) (4) of patients, respectively. Thus, we recommend removing this adverse reaction from Table 2 to be consistent with the title of Table 2 if this is still the case after the sponsor updates the adverse reactions based on the response to the IR.
USE IN SPECIFIC POPULATIONS **8.5 Geriatric Use**	Of the 112 patients with relapsed or refractory AML with a NPM1 mutation treated with KOMZIFTI, 70 (63%) patients were 65 years of age or older, and 31 (278) were 75 years or older.	Please revise the percentage of patients who were 75 years or older, as we note it currently reads as "278" %.
CLINICAL PHARMACOLOGY **12.3 Pharmacokinetics**	**Table 11. Ziftomenib Pharmacokinetics in Patients with R/R AML**	We note that the table prior to this table is titled as Table 3. Thus, OPDP recommends revising the

		table number in this title to 4. OPDP also recommends then evaluating the remainder of the table numbers throughout the FPI and making the appropriate revisions.
PATIENT COUNSELING INFORMATION <u>Differentiation Syndrome</u>	Advise patients of the risk of developing differentiation syndrome as early as (b) (4) after the start of therapy and during treatment. Instruct patients to immediately report any symptoms suggestive of differentiation syndrome, such as fever, joint or bone pain, dizziness, shortness of breath or difficulty breathing, cough, chest pain, rapid weight gain, rash, decreased urinary output, or swelling in the hands, feet, ankles, or legs, to their healthcare provider for further evaluation *[see Boxed Warning and Warnings and Precautions (5.1)]*.	We note that the approved labeling for another menin inhibitor indicated for R/R AML, Revuforj, and other products indicated for R/R AML, including Rezlidhia, Tibsovo, and Xospata, all specifically include the symptom of “low blood pressure” for patient counseling pertaining to differentiation syndrome. For consistency with the other labels and to prevent minimization of risk, we recommend including this symptom, but we defer to DHM1.

23 Pages of Draft Labeling 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/

SAMIA ALAM
09/09/2025 01:20:12 PM

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

PATIENT LABELING REVIEW

Date:	September 8, 2025
To:	Amy Baird Regulatory Project Manager **Division of Hematologic Malignancies I (DHM1)**
Through:	Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samia Alam, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	KOMZIFTI (ziftomenib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 220305
Applicant:	Kura Oncology, Inc.

1 INTRODUCTION

On March 31, 2025, Kura Oncology, Inc. submitted for the Agency's review an original New Drug Application (NDA) 220305 for KOMZIFTI (ziftomenib) capsules. The proposed indication is for the treatment of adults with relapsed or refractory (R/R) acute myeloid leukemia (AML) with a nucleophosmin 1 (NPM1) mutation.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies I (DHM1) on May 21, 2025, and April 11, 2025, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for KOMZIFTI (ziftomenib) capsules.

2 MATERIAL REVIEWED

- Draft KOMZIFTI (ziftomenib) capsules MG received on March 31, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 29, 2025.
- Draft KOMZIFTI (ziftomenib) capsules Prescribing Information (PI) received on March 31, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 29, 2025.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

5 Pages of Draft Labeling 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/

HELEN K YOUNG
09/08/2025 01:49:03 PM

SAMIA ALAM
09/08/2025 02:35:40 PM

BARBARA A FULLER
09/08/2025 03:20:29 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	August 28, 2025
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 220305
Product Name, Dosage Form, and Strength:	Komzifti (ziftomenib) capsules, 200 mg
Applicant Name:	Kura Oncology, Inc.
FDA Received Date:	August 21, 2025
TTT ID #:	2025-14062-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Kura Oncology, Inc. submitted a revised container label received on August 21, 2025 for Komzifti. We reviewed the revised container label for Komzifti (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Kura Oncology, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kundreskas, J. Label and Labeling Review for Komzifti (NDA 220305). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 AUG 7. TTT ID: 2025-14062.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON AUGUST 21, 2025

Container Label:

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/

JODY K KUNDRESKAS
08/28/2025 07:03:12 AM

NICOLE F IVERSON
08/28/2025 09:42:56 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	August 7, 2025
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 220305
Product Name, Dosage Form, and Strength:	Komzifti (ziftomenib) capsules, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Kura Oncology, Inc.
FDA Received Date:	March 31, 2025 and August 1, 2025
TTT ID #:	2025-14062
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

As part of the approval process for Komzifti (ziftomenib) capsules, we reviewed the proposed Komzifti Prescribing Information (PI), Medication Guide (MG), and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI), Medication Guide (MG), and container label for areas of vulnerability that may lead to medication errors and other areas of improvement.

We noted a discrepancy between the proposed How Supplied section of the PI and the Container Closure System document[a] submitted as part of the application, and we requested that the Office of Pharmaceutical Quality (OPQ) address the discrepancy with the Applicant. In their response[b] to OPQ's inquiry regarding packaging configurations, the Applicant stated that they intend to market only the 90-count bottle as listed in the PI.

Additionally, we noted that the MG states to (b) (4) however, the storage information in Section 16 of the PI and the container label do not convey this information. We requested OPQ confirm how the product should be stored and dispensed. OPQ confirmed that (b) (4) . Thus, we provide a recommendation for the Applicant to remove reference to (b) (4)

Lastly, we noted that Section 2.4 *Dosage Modifications for Adverse Reactions* of the PI, states "Interrupt dosing or reduce dose for adverse reactions as per Table 1.", however, Table 1 does

[a] Container Closure System for Ziftomenib (NDA 220305). San Diego (CA): Kura Oncology, Inc.; 2025 MAR 31. Available from: \\CDSESUB1\EVSPROD\nda220305\0001\m3\32-body-data\32p-drug-prod\ziftomenib\32p7-cont-closure-sys\container-closure-system.pdf.

[b] Response to July 25, 2025 Information Request (IR) for ziftomenib (NDA 220305). San Diego (CA): Kura Oncology, Inc.; 2025 AUG 01. Available from: \\CDSESUB1\EVSPROD\nda220305\0023\m1\us\response-to-fda-cmc-ir7-dated-july-25.pdf.

not list any dose reduction actions, which may lead to wrong dose medication errors. We reached out to the clinical review team to address this discrepancy.

4 CONCLUSION

The proposed Komzifti Prescribing Information (PI), Medication Guide (MG), and container label may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Hematologic Malignancies 1 (DHM 1) in Section 5 and for Kura Oncology, Inc. in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Prescribing Information
    1. Section 2 Dosage and Administration
        a. As currently presented in Section 2.3 *Administration*, the instructions for what to do for missed doses discovered less than 12 hours prior to the next scheduled dose are missing. Failure to provide instructions for all scenarios may lead to dosing errors. We recommend clarifying what to do if the missed dose is discovered less than 12 hours prior to the next scheduled dose.
    2. Section 16 How Supplied/Storage and Handling
        a. As currently presented, the storage conditions are not presented consistently within Section 16 (i.e., regular storage conditions are presented in Fahrenheit first followed by Celsius in parenthesis, but excursions are presented in Celsius first followed by Fahrenheit in parenthesis) and are inconsistent with the presentation of the storage conditions located on the container label (in Celsius first followed by Fahrenheit in parenthesis for both regular and excursion storage conditions). Inconsistencies in storage presentation may contribute to confusion and deteriorated drug medication errors. We recommend revising the storage conditions so that they are presented consistently throughout Section 16 and the container label.
    3. Section 17 Patient Counseling
        a. We recommend revising the language used in the second bullet under Dosing Instructions so that it aligns with the presentation of the same information in Section 2.3. Revise to “Advise patients to swallow KOMZIFTI capsules whole. Do not open, break, or chew the capsules.”.
        b. As currently presented, the instructions for what to do for missed doses discovered less than 12 hours prior to the next scheduled dose are missing. Failure to provide instructions for all scenarios may lead to dosing errors. We recommend clarifying what to do if the missed dose is discovered less than 12 hours prior to the next scheduled dose.

B. Medication Guide (MG)

1. We note that the pronunciation of the proprietary name KOMZIFTI is listed in the MG as (b) (4) which does not align with the pronunciation in the Request for Proprietary Name Review. We recommend revising the pronunciation to align with the pronunciation provided in the Request for Proprietary Name Review.
2. We recommend revising the language used in the fifth bullet under How should I take KOMZIFTI? so that it aligns with the presentation of the same information in Section 2.3. Revise to "Swallow KOMZIFTI capsules whole. Do not open, break, or chew the capsules.".
3. As currently presented in the sixth bullet under How should I take KOMZIFTI?, the instructions for what to do for missed doses discovered less than 12 hours prior to the next scheduled dose are missing. Failure to provide instructions for all scenarios may lead to dosing errors. We recommend clarifying what to do if the missed dose is discovered less than 12 hours prior to the next scheduled dose.
4. As currently presented in What are the possible side effects of KOMZIFTI? the sentence "Your healthcare provider may decrease your dose, temporarily stop, or completely stop your treatment with KOMZIFTI if you develop certain side effects during treatment with KOMZIFTI." does not align with the information in Section 2.4 of the PI. This may lead to confusion and dosing errors. We recommend aligning information on dose reduction with the information presented in the PI.
5. Under How should I store KOMZIFTI?, the MG states to (b) (4) , however, the storage information in Section 16 of the PI does not convey this information. Inconsistent storage and handling information may result in confusion and deteriorated drug medication errors. We recommend revising the storage information in the MG so that it is consistent with the rest of the labeling.

6 RECOMMENDATIONS FOR KURA ONCOLOGY, INC.

A. Container Label

1. As currently presented, the established name lacks prominence on the Principal Display Panel (PDP) due to the grey font color used. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. We recommend increasing the prominence of the established name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
2. As currently presented, there is insufficient contrast between the (b) (4) font color used for the dosage form "capsules" and the white background of the PDP, which makes the text difficult to read. We recommend you revise the colors to

improve the contrast between the font and the background color to improve readability and legibility of the dosage form.

3. As currently presented, the (b) (4) diamond shaped graphic competes with the prominence of critical information such as the established name and product strength on the PDP. The proprietary name and established name along with the product strength, and warnings or cautionary statements should be the most prominent information on the PDP. Furthermore, see 21 CFR 201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter. Decrease the prominence of your graphic relative to the prominence of the critical information on the PDP needed for proper identification and use of your proposed product in accordance with 21 CFR 201.15(a)(6). For example, this may be accomplished through increasing the prominence of the strength statement and minimizing the size of the graphic itself or relocating the graphic to another panel.
4. As currently presented, the manufacturer information (e.g., KURA ONCOLOGY and KYOWA KIRIN) competes in prominence with critical product information (e.g., strength) on the PDP. Critical product information such as the proprietary name, established name, and product strength should appear as the most prominent information on the PDP in accordance with 21 CFR 201.15. Reduce the size of or move the manufacturer information to the side panel so it does not compete with the prominence of important product information on the PDP. Alternatively, the prominence of the strength may be increased.
5. We note the inclusion of a Medication Guide (MG) as part of the labeling submission; however, the MG statement is missing from the PDP of the container label. Per 21 CFR 208.24(d), the label of each container of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner. Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d).
6. As currently presented, the administration technique, "Swallow capsules whole. Do not open, break, or chew the capsules." is provided in the Prescribing Information (PI); however, it is missing from the container. To ensure the capsules are administered correctly, we recommend adding the statement "Swallow capsules whole. Do not open, break, or chew the capsules." to the PDP or side panel of the container label.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Komzifti received on March 31, 2025 from Kura Oncology, Inc.

Table 2. Relevant Product Information for Komzifti	
Initial Approval Date	N/A
Active Ingredient	ziftomenib
Indication	for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a nucleophosmin 1 (NPM1) mutation.
Dosage Form	capsules
Strength	200 mg
Route of Administration	oral
Dose and Frequency	600 mg taken orally once daily until disease progression or unacceptable toxicity. For patients without confirmed disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response.
How Supplied	KOMZIFTI 200 mg capsules are supplied as white, (b) (4) hypromellose capsules printed with "ZIF 200" in black ink. KOMZIFTI capsules are available in white, induction-sealed, square, high-density polyethylene bottles of 90 capsules with child-resistant closure (NDC 84696-200-90).
Storage	Store at 68°F to 77°F (20°C to 25°C); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
Container Closure	(b) (4)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Komzifti labels and labeling submitted by Kura Oncology, Inc.

- Prescribing Information and Medication Guide received on March 31, 2025, available from \\CDSESUB1\EVSPROD\nda220305\0001\m1\us\komzifti-ziftomenib-final-proposed-clean-uspi.pdf

B.2 Container Label Image

Container Label:

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On April 15, 2025, we searched for previous DMEPA reviews relevant to this current review using the terms, ‘Komzifti’, ‘ziftomenib’, ‘220305’, and ‘142028’. Our search identified no previous reviews.

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/

JODY K KUNDRESKAS
08/07/2025 06:33:40 AM

NICOLE F IVERSON
08/07/2025 10:06:51 AM

CLINICAL INSPECTION SUMMARY

Date	July 25, 2025
From	Anthony Orencia, M.D., Ph.D., F.A.C.P., Senior Physician Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., F.A.A.P., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Joseph P. Wynne, M.D., Ph.D., Senior Physician Cara A. Rabik, M.D., Medical Team Leader Amy C. Baird, Supervisory Regulatory Project Manager R. Angelo de Claro, M.D., Division Director, Division of Hematologic Malignancy 1, and Acting Office of Oncology Drugs Director, Office of New Drugs, CDER Oncology Drugs
NDA	NDA 220305
Applicant	Kura Oncology, Inc.
Drug	Ziftomenib
NME	Yes
Classification	Menin inhibitor
Proposed Indications	For the treatment of adult patients with relapsed or refractory acute myeloid leukemia with a nucleophosmin mutation
Review Type	Priority
Consultation Request Date	May 14, 2025
Summary Goal Date	July 31, 2025
Action Goal Date	October 30, 2025
PDUFA Date	November 30, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study KO-MEN-001 were submitted to the Agency in support of a New Drug Application (NDA) for ziftomenib, indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a nucleophosmin (NPM1) mutation.

Inspections of clinical investigators (Amir Fathi, M.D., and James Foran, M.D.) and the sponsor, Kura Oncology, were conducted. Based on the results of the completed inspections, the study data derived from the above inspected clinical investigator sites and submitted by the sponsor are considered acceptable. The sponsor's oversight and monitoring for the study appears adequate.

In general, the clinical data submitted to the Agency for assessment appear to be acceptable in support of the proposed indication.

II. BACKGROUND

Ziftomenib is a menin inhibitor works by inhibiting the interaction between the menin protein and the MLL (KMT2A) fusion protein. The potential for this drug holds some promise for inhibition of cellular growth for acute myeloid leukemia especially in patients with a nucleophosmin mutation with aggressive form of leukemia that portends a poor prognosis.

Study KO-MEN-001 was a Phase 1 to 2 first in human, open-label, dose expansion, dose validation and dose optimization multicenter, multiple cohort clinical investigative study of ziftomenib in subjects ≥18 years of age with relapsed/refractory acute myeloid leukemia. Subjects were administered ziftomenib orally once daily continually.

Phase 1 Part 1a:
The primary objective of the dose-escalation phase of the study was to determine the maximum tolerated dose and to select doses for evaluation in Part 1b dose-expansion/validation for recommended Phase 2 dose optimization.

The secondary objectives were to evaluate the safety and tolerability of ziftomenib in patients with R/R AML based on National Cancer Institute Common Terminology Criteria for Adverse Events v5.0, characterize the pharmacokinetics of ziftomenib and its metabolites after single and multiple oral dose administrations, and explore early evidence of anti-leukemic activity using criteria from the 2017 European Leukemia Network (ELN) Recommendations for acute myeloid leukemia and the US FDA 2020 Guidance for Industry.

Phase 1 Part 1b:
The primary objective of the dose-validation/expansion phase was to determine the safety, tolerability, and minimum biologically effective dose of ziftomenib in patients with nucleophosmin 1-mutant (NPM1-m) and Lysins[K]-specific methyltransferase 2 rearranged (KMT2A-r) AML to support selection of registrational Phase 2 portion of the study (i.e., recommended Phase 2 dose).

The secondary objectives were to explore early evidence of anti-leukemia activity of ziftomenib in patients with relapsed/refractory acute myeloid leukemia using the criteria outlined in the 2017 ELN Recommendations for acute myeloid leukemia and the US FDA Guidance for Industry for acute myeloid leukemia.

Phase 2:
The primary objective of registrational Phase 2 portion of this study was to assess evidence of anti-leukemia activity of ziftomenib according to criteria proposed by the 2022 ELN Recommendations for acute myeloid leukemia and the US FDA Guidance for Industry for acute myeloid leukemia in patients with NPM1-m relapsed/refractory acute myeloid leukemia.

The secondary objectives were to assess the clinical activity, safety, and tolerability of ziftomenib in patients with NPM1-m relapsed/refractory acute myeloid leukemia. Additionally, further exploration

of clinical activity was conducted based on the criteria proposed by the 2022 ELN Recommendations for acute myeloid leukemia and the US FDA Guidance for Industry for acute myeloid leukemia.

The primary efficacy endpoint of Phase 2 part comprised complete remission (CR) or complete remission with hematologic recovery (CRh).

The primary safety endpoint involves comprehensive adverse event assessment.

For this Phase 1 to 2 study, there were 92 subjects enrolled in Phase 2 part from 56 centers in eight countries. The start dates of the study were September 5, 2019 for Phase 1, and January 23, 2023 for Phase 2. The data cutoff date was October 28, 2024.

III. RESULTS

1. **Amir T. Fathi, M.D./ Site #105**
   Massachusetts General Hospital
   55 Fruit Street, Suite 8B
   Boston, MA 02114

   Inspection dates: July 10-18, 2025

   The site enrolled 9 adult study subjects. Eight study subjects completed the study. All subject records were reviewed for the Phase 2 study.

   This comprehensive inspection covered the following areas: documentation of informed consent, eligibility criteria, adverse events, treatment with the investigational product, laboratory results, selected questionnaire results and source data for subject visits, Institutional Review Board approvals, communication with the sponsor, and selected monitoring activities. Source records were a combination of hard copy paper records and printed electronic medical records.

   The primary efficacy endpoint data were verified. No data discrepancies were observed.

   No safety issues or under-reporting of adverse events were observed at this clinical investigator site.

   Based on this preliminary inspectional result, no significant Good Clinical Practice (GCP) deviations were reported. A follow-up summary report will be amended if there are any significant changes in the final inspection report.

2. **James Foran, M.D./ Site # 112**
   Mayo Clinic Florida
   4500 San Pablo Road
   Jacksonville, FL 32224

Inspection dates: June 16-20, 2025

A total of seven adult subjects who were screened; six study subjects enrolled. Three study subjects completed the treatment phase of the study. The data for four of the six enrolled subjects were reviewed in the Phase 2 study.

This comprehensive inspection covered the following areas: records for participant informed consent forms (ICFs), signed investigator agreements, financial disclosure statements, site training, Institutional Review Board submissions and correspondence, adverse event and serious adverse event reporting, imaging and laboratory reports, clinical source data, electronic data capturing system information, and monitoring activities for the inspected protocol.

Electronic records replaced most paper source documents at this site. Mayo Clinic utilizes EPIC electronic medical record for all source data recording and transcribes it into the electronic data capture system, iMedidata and Rave repositories. FDA reviewed read-only access to Rave, Florence, EPIC, and Vestigo electronic systems. Vestigo was utilized by the research pharmacy for drug accountability, storage of temperature logs, and pharmacy staff training documents.

The primary efficacy endpoint was verifiable.

No under-reporting of serious adverse events or adverse events were found.

The following observations were identified during the inspection:
(a) Subject (b) (6) did not have LDH labs assessed on treatments Cycle 1 Day 10 and 15, respectively and Cycle 2 Day 1.
(b) Subject (b) (6) lacked a bone marrow aspirate sample collection at the end of treatment visit on (b) (6) Additionally, pre-dose vitals collection and documentation dated (b) (6) s not attributable to the person collecting and documenting the information.
(c) Subjects (b) (6) had corrected electrocardiogram dates are not attributable to the person completing, or date of the correction.
(d) Subjects (b) (6) had in-clinic dosing documentation on the subject dosing diary not attributable to the person documenting dose date, number of pills, and time.

Reviewer's Comments:
These observations are mainly attributed to reporting and record accuracies and were considered minor; and their impact on evaluation of the primary efficacy results is less likely to be significant. On July 14, 2025, Dr. Foran provided a response and corrective and preventive action plans. The response appeared adequate.

3. Kura Oncology, Inc.
12730 High Bluff Drive, Suite 400
San Diego, CA 92130

Inspection dates: June 23 - 27, 2025

FDA inspection reviewed records including standard operating policies and procedures, task orders, monitoring plans, medical monitoring plans, safety management plans, data management plans, site corrective and preventive action plans, monitoring visit reports, Interactive Response Technology (IRT) subject listings, user access reports for IRT, protocol deviation listings, and vendor listings. Steps such as retraining of site staff were taken by a contracted CRO to promote compliance.

The monitoring files for Sites # 302, #304, #101 and #105 were reviewed and found to be adequate. No under-reporting of adverse events was found.

Based on this preliminary report, study oversight and general monitoring by sponsor appeared adequate. An addendum to this summary will be filed if there are significant changes in the final inspection report.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D., F.A.C.P.
FDA Senior Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Medical Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Jenn Sellers, M.D., Ph.D., F.A.A.P.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/

ANTHONY J ORENCIA
07/31/2025 05:25:36 AM

MIN LU
07/31/2025 07:50:11 AM

JENN W SELLERS
07/31/2025 09:11:26 AM