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RESEARCH**

APPLICATION NUMBER:

220305Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA Multidisciplinary Review and Evaluation

NDA 220305

Komzifti (ziftomenib)

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NME
Application Number(s)	NDA 220305
Priority or Standard	Priority
Submit Date(s)	March 31, 2025
Received Date(s)	March 31, 2025
PDUFA Goal Date	November 30, 2025
Division/Office	Office of Oncologic Diseases/Division of Hematologic Malignancies I
Review Completion Date	November 12, 2025
Established Name	Ziftomenib
(Proposed) Trade Name	KOMZIFTI
Pharmacologic Class	Small molecule menin inhibitor
Applicant	Kura Oncology, Inc.
Formulation(s)	200 mg capsules
Dosing Regimen	600 mg daily
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with nucleophosmin 1 (NPM1) mutation
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	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
SNOMED CT for the Indicated Population	703820005 763309005

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRM=Division of Risk Management

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Glossary

AC	advisory committee	ECG	electrocardiogram
ADME	absorption, distribution, metabolism, excretion	eCTD	electronic common technical document
AE	adverse event	E-R	Exposure-response
AML	acute myeloid leukemia	ESS	effective sample size
ARA	Gastric acid reducing agent	ETASU	elements to assure safe use
AST	Aspartate aminotransferase	FDA	Food and Drug Administration
BA	Bioavailability	FDAAA	Food and Drug Administration Amendments Act of 2007
BLA	biologics license application	FDASIA	Food and Drug Administration Safety and Innovation Act
BPCA	Best Pharmaceuticals for Children Act	GCP	good clinical practice
BRF	Benefit Risk Framework	GLP	good laboratory practice
CBER	Center for Biologics Evaluation and Research	GRMP	good review management practice
CDER	Center for Drug Evaluation and Research	GT	Grouped terms
CDRH	Center for Devices and Radiological Health	HI	Hepatic impairment
CDTL	Cross-Discipline Team Leader	HSCT	Hematopoietic stem cell transplantation
CFR	Code of Federal Regulations	ICH	International Conference on Harmonization
CI	Confidence interval	ITT	intent to treat
CL _{CR}	Creatinine clearance	KMT2A	Lysine methyltransferase 2A
CMC	chemistry, manufacturing, and controls	KMT2Ar	Lysine methyltransferase 2A rearrangement
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms	MedDRA	Medical Dictionary for Regulatory Activities
CR	Complete remission	mITT	modified intent to treat
CRh	CR with partial hematologic recovery	NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
CRF	case report form	NDA	new drug application
CRO	contract research organization	NME	new molecular entity
CRT	clinical review template	NPM1	nucleophosmin 1
CSR	clinical study report	NPM1c	Cytoplasmic location of NPM1
CSS	Controlled Substance Staff	NPM1m	NPM1 mutated
DDI	Drug-drug interaction	OSE	Office of Surveillance and Epidemiology
DMC	data monitoring committee	OSI	Office of Scientific Investigation
D-R	Dose-response	PBRER	Periodic Benefit-Risk Evaluation Report
DS	Differentiation syndrome	PD	pharmacodynamics

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P-gp	P-glycoprotein	REMS	risk evaluation and mitigation strategy
PI	prescribing information	RI	Renal impairment
PK	pharmacokinetics	R/R	Relapsed or refractory
PMC	postmarketing commitment	SAE	serious adverse event
PMR	postmarketing requirement	SAP	statistical analysis plan
PP	per protocol	SEE	Substantial evidence of effectiveness
PPI	patient package insert	SGE	special government employee
PREA	Pediatric Research Equity Act	SOC	standard of care
PRO	patient reported outcome	TEAE	treatment emergent adverse event
PSUR	Periodic Safety Update report	TI	Transfusion independence
PT	Preferred term	ULN	Upper limit of normal

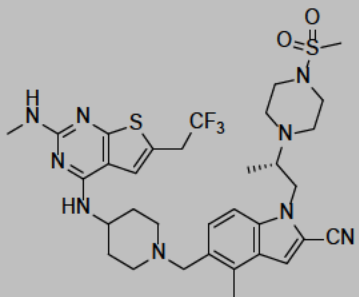
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1 Executive Summary

1.1. Product Introduction

Proposed Trade Name:	Komzifti	
Established Name:	Ziftomenib	
Also Known As:	KO-539	
Chemical Name:	(S)-4-methyl-5-(((4-((2-(methylamino)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1-(2-(4-(methylsulfonyl)piperazin-1-yl)propyl)-1H-indole-2-carbonitrile	
Molecular Formula:	C ₃₃ H ₄₂ F ₃ N ₉ O ₂ S ₂	Chemical Structure 
Molecular Weight:	717.88 g/mol	
Dosage Forms:	200 mg capsule	
Therapeutic Class:	Antineoplastic	
Chemical Class:	Small molecule	
Pharmacologic Class:	Menin inhibitor	

Mechanism of Action: Ziftomenib is a menin inhibitor that blocks that interaction of menin and lysine [K]-specific methyltransferase 2A (KMT2A). By disrupting the interactions between menin and KMT2A (wild-type or rearranged), menin inhibitors disrupt the leukemogenic transcriptional signaling induced by chromatin-binding complexes that are facilitated by and contain menin and rearranged KMT2A. NPM1 is a multifunctional protein that typically resides in the nucleolus but becomes mainly cytosolic and a leukemogenic driver when it is mutated (NPM1c). The leukemogenic activity of NPM1c is mediated by the activity of the menin/KMT2A (wild-type or rearranged) chromatin-modulating complex and is inhibited by the activity of menin inhibitors.

Ziftomenib is a new molecular entity (NME). NDA 220305 was submitted under the 505(b)(1) pathway for the proposed indication of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a nucleophosmin 1 (*NPM1*) mutation using a dose of 600 mg daily.

The review team recommends approval of ziftomenib with an indication of “treatment of adult

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patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible nucleophosmin 1 (*NPM1*) mutation who have no satisfactory alternative treatment options” using a dose of 600 mg daily. The recommendation is based on the findings in Study KO-MEN-001 of a 21.4% CR + CRh rate, median duration of CR + CRh of 5.0 months, and a 21% conversion rate to transfusion independence (TI). Additional studies are warranted to confirm safety with long-term use, to establish the appropriate dosage in pediatric patients, to establish the appropriate dosage(s) in patients with organ impairment, and to assess for potential drug interactions. Development of a companion diagnostic (CDx) to select patients with susceptible *NPM1* mutations is recommended.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Study KO-MEN-001 (KOMET-001, NCT NCT04067336) was an open-label, Phase 1-2, multiple cohort, multicenter study of ziftomenib monotherapy in adult patients ≥ 18 years of age with relapsed or refractory (R/R) acute myeloid leukemia (AML) harboring a mutation in the *NPM1* gene (*NPM1m*). Patients in the pivotal cohort of the study were required to have *NPM1* mutations classified as A, B, or D subtypes; other mutations in *NPM1* were permitted if they were reasonably likely to lead to cytoplasmic localization of the NPM1 protein. Treatment consisted of ziftomenib at a dose of 600 mg daily until disease progression or unacceptable toxicity.

The Phase 1 portion was an open-label, dose-escalation study for patients with non-genetically defined R/R AML; seven single arm cohorts evaluated ziftomenib dosages between 50 and 1000 mg daily (n=30). The Phase 1b portion sought to optimize the dosage of ziftomenib and compared two dosages (200 mg daily, n=17, and 600 mg daily, n=36) in patients with R/R *NPM1m* AML. The Phase 2 portion enrolled 92 patients with R/R *NPM1m* AML treated at a ziftomenib dosage of 600 mg daily. Local testing was used for diagnosis and enrollment. The primary objective of the Phase 2 portion was determination of the CR + CRh rate.

The pivotal cohort was the population of study participants enrolled in the Phase 2 portion of the study (n=92). This cohort demonstrated a CR + CRh rate of 18.5% (95% confidence interval: 11.1%, 27.9%), with a median DoR of 4.6 months (range 0 to 14.7+ months). Of note, after adjudication of responses, the lower bound of the CI did not exclude the null hypothesis of 12%. However, the efficacy data were considered meaningful in a patient population with no satisfactory alternative treatment options.

Supportive confirmatory data was provided by the Phase 1b portion of KO-MEN-001 (n=20), which had a CR + CRh rate of 35% (95% CI 15.4, 59.2%), with DoR of 5.6 months (range 1.0-13.8 months).

Due to the similarities between the Phase 1b and Phase 2 patient populations, the labeled population includes an analysis of all patients in the Phase 1b and Phase 2 portions of the study who received treatment with the recommended dosage of ziftomenib. This population included 112 participants with R/R AML. The median number of prior lines of therapy was 2. In this

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population, the CR + CRh rate was 21.4%, the median duration of CR + CRh was 5.0 months, and the rate of conversion to 56-day transfusion independent (TI-56) was 21.2%. The FDA team noted the low point estimates for CR + CRh and TI-56 rates, along with the short duration of response. There was a short duration of treatment (median 2.2 months), with only 19% of participants receiving at least 6 months of ziftomenib therapy. As targeted monotherapy may require additional time on therapy to achieve response, this limited treatment duration may underestimate the true response rate in the indicated patient population.

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence. The relatively low CR + CRh rate, low TI rate, and short follow-up limiting assessment of durability leads to some uncertainty about clinical benefit. However, the results from the Phase 2 efficacy cohort of Study KO-MEN-001 and the additional confirmatory data from the Phase 1b portion of KO-MEN-001 are considered substantial evidence of effectiveness of ziftomenib for the treatment of R/R AML with a susceptible *NPM1* mutation who have no satisfactory alternative treatment options.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

R/R AML presents a therapeutic challenge. While curative options exist, these involve the use of intensive chemotherapy followed by hematopoietic stem cell transplantation (HSCT), which are not available options for older, frailer patients. The median age of diagnosis of AML is 68 years; at the time of relapse, many patients are not considered eligible for this intensive, curative therapy. As such, there remains an unmet medical need for patients with R/R AML. Study KO-MEN-001 was a multiple-cohort dose-escalation and dose-expansion trial that included 112 participants treated with ziftomenib at the recommended dose of 600 mg daily. In the combined Phase 1b (dose expansion) + Phase 2 (pivotal) cohort, which comprises the labeled patient population, the CR + CRh rate was 21.4%, the median DoR was 5.0 months, and the TI-56 rate was 21.2%. The review team noted that these low rates required careful consideration of the overall benefit-risk assessment.

The safety population included the 112 patients in the Phase 1b + Phase 2 cohort treated at the recommended dosage. The median duration of exposure was 2.2 months (range 0.1-21.5 months); 18% of participants received treatment with ziftomenib for > 6 months.

Fatal adverse reactions (ARs) occurred in 4 (4%) participants, including 2 with fatal differentiation syndrome (DS), 1 with infection, and 1 with sudden death. Dosage interruption due to AR occurred in 54% of participants, dose reduction due to an AR in 4% of participants, and discontinuation of ziftomenib due to an AR in 21% of participants. DS occurred in 26% of participants, and QTc prolongation occurred in 12% of participants. Median dose intensity was > 90% in both the Phase 1b and Phase 2 portions of the study, indicating that the recommended dose of 600 mg daily is tolerable. However, the high rates of DS and high rate

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of dosage interruption indicate a need to mitigate ARs in labeling.

The Division determined that the totality of evidence, including the observed CR + CRh and TI-56 rates, the overall DoR, and the safety profile, supports a positive benefit-risk assessment of ziftomenib at this time for adult patients with R/R AML with a susceptible *NPM1* mutation who have no satisfactory alternative treatment options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	R/R AML is a fatal disease if untreated.	R/R AML is a fatal disease, including R/R AML with an <i>NPM1</i> mutation
Current Treatment Options	- At the time of the NDA submission, there were no drugs approved specifically for patients with R/R AML with an <i>NPM1</i> mutation. - The standard of care for R/R AML is intensive chemotherapy followed by HSCT; however, many patients are older and frailer and cannot tolerate this paradigm. - Gemtuzumab ozogamicin is approved for patients with R/R AML with CD33 expression; however, its use is limited by its toxicity profile, including veno-occlusive disease and infectious complications. - Co-mutations in other genes, including <i>FLT3</i>, <i>IDH1</i>, and <i>IDH2</i> have additional approved agents; however, these are not curative.	New treatments are needed to improve survival of patients with <i>NPM1</i> mutated AML that has relapsed or is refractory to initial treatment.
Benefit	- KO-MEN-001 was a multiple cohort, dose-escalation and expansion study that included 112 participants with R/R <i>NPM1m</i> AML treated with ziftomenib at a dosage of 600 mg daily. - The CR + CRh rate was 21.4% (95% CI 14.2, 30.2) with a median Do(CR+CRh) of 5.0 months (95% CI 1.9, 8.1). - The rate of TI-56 was 21.2% (95% CI 12.1%, 33.0%). - Approximately 30% of participants enrolled in the study had a mutation in <i>NPM1</i> other than the A, B, and D subtypes.	Ziftomenib at a dose of 600 mg daily is active in the treatment of R/R AML with a susceptible <i>NPM1m</i> .
Risk and Risk Management	- Fatal adverse reactions included differentiation syndrome (DS), infection, and sudden death. - DS occurred in 26% and QTc prolongation in 12%. - Adverse reactions resulted in dose reduction in 54% and treatment discontinuation in 21% of participants.	The safety profile of ziftomenib appears generally acceptable in the short term, as administered in the study KO-MEN-001. Serious risks of differentiation syndrome and QTc

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The most common adverse reactions ($\geq 20\%$) included: infection without an identified pathogen, hemorrhage, diarrhea, nausea, fatigue, edema, bacterial infection, musculoskeletal pain, differentiation syndrome (DS), pruritus, febrile neutropenia, and transaminases increased. • The safety of long-term use of ziftomenib has not been established. • There is insufficient information regarding toxicities of ziftomenib with potential drug-drug interactions (DDI) and in patients with severe renal or hepatic impairment. • A safe and effective dose has not been established in patients < 18 years of age. • The clinical trials included specific monitoring to mitigate serious toxicities, including DS and QTc prolongation.	prolongation should be mitigated with appropriate labeling. Additional studies are needed to establish safe dosing for long-term use, in pediatric patients, and in special populations.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

□ The patient experience data that was submitted as part of the application, include: □ Clinical outcome assessment (COA) data, such as □ Patient reported outcome (PRO) □ Observer reported outcome (ObsRO) □ Clinician reported outcome (ClinRO) □ Performance outcome (PerfO) □ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) □ Patient-focused drug development or other stakeholder meeting summary reports □ Observational survey studies designed to capture patient experience data □ Natural history studies	Section where discussed, if applicable [e.g., Section 6.1 Study endpoints] [e.g., Section 2.1 Analysis of Condition]

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- Patient preference studies (e.g., submitted studies or scientific publications)
- Other: (Please specify)
- Patient experience data that was not submitted in the application, but was considered in this review.

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Acute myeloid leukemia (AML) is a rapidly progressing and heterogeneous hematopoietic disease arising from genetic and epigenetic dysregulation in hematopoietic precursor cells leading to the clonal proliferation of myeloid precursors with an inability to differentiate into more mature cellular elements. As a result, there is an accumulation of these immature cells (ie, leukemic blasts) in the bone marrow, peripheral blood, and occasionally in other tissues, with a variable reduction in the production of normal red blood cells (RBCs), platelets, and mature granulocytes. The increased production of malignant cells, along with a reduction in these mature elements, results in a variety of systemic consequences. The clinical manifestations include cytopenias, bleeding or bruising, fatigue, and an increased risk of infection, which may all be accompanied by constitutional symptoms, metabolic abnormalities, and various other complications.

Although AML is the most common form of acute leukemia in adults, it is a relatively rare disease. AML accounts for nearly 2% of all adult cancer deaths in the United States (US). In 2024, 20,800 people were estimated to be diagnosed with AML, and 11,220 were expected to die from AML (NCI, 2023). The median age at diagnosis is 69 years of age in adults, with approximately 60% of patients diagnosed at ≥ 65 years of age and one-third of patients diagnosed at ≥ 75 years of age. Overall, AML is a heterogeneous disease in which high initial response rates are observed followed by frequent relapse. More than half of patients who achieve complete remission (CR) following induction therapy will eventually relapse within 1 to 3 years, and only 31.9% of patients with AML in the US will survive ≥ 5 years (Kumar, 2011; NCI, 2023). With relapse, survival outcomes decline drastically; $<10\%$ of patients with relapsed or refractory (R/R) AML will survive ≥ 3 years (Brandwein et al, 2020).

Nucleophosmin-1 (*NPM1*) is an essential driver of and the most commonly mutated gene in AML, occurring in approximately 30% (ie, 6240) of new adult AML cases in the US annually (Döhner et al, 2017; NCI, 2023). *NPM1* mutation (*NPM1-m*) is also detected in 91% of *NPM1-m*

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patients at relapse, many years after initial diagnosis (Chen and Hu, 2020; Cocciardi et al, 2019). Thus, *NPM1*-m is a consistent marker of the disease. The mechanism by which mutations in *NPM1* transform healthy hematopoietic cells into leukemia is incompletely understood. Nonetheless, several studies have demonstrated a critical role of the menin/mixed lineage leukemia (MLL) (lysine [K]-specific methyltransferase 2A) (*KMT2A*) complex in leukemogenesis mediated by *NPM1*-m (Klossowski et al, 2020; Kühn et al, 2016; Tibsovo® USPI). Thus, there is a strong rationale for targeting acute leukemia genetic subsets that require menin-MLL(*KMT2A*) interaction, such as in *NPM1*-m AML.

Patients with *NPM1*-m AML who relapse have a dismal prognosis, with a median aggregate overall survival (OS) of 6.1 months and a worsening survival outcome with each subsequent line of therapy. For patients receiving their third line of therapy or greater, median OS is between 5.3 and 3.5 months, respectively (Issa et al, 2023). Notably, these outcomes are seen in patients from a single large referral center with more than half of the patients receiving multiagent therapy and a third receiving intensive chemotherapy. Patients in Study KO-MEN-001 were ineligible to receive these multiagent or intensive chemotherapies. Results from Issa et al, 2023 are a potential over estimation of the expected outcomes for the proposed intended patient population.

In addition, relapse occurs faster with each subsequent line of therapy as indicated by a retrospective analysis of 206 *NPM1*-m AML patients, with median relapse-free survival (RFS) was as low as 3.3 months in the R/R setting (Issa et al, 2023). While *NPM1*-m AML may be associated with a more favorable prognosis compared with other genetic subvariants in newly diagnosed patients, there was no significant difference in RFS or OS among patients with R/R *NPM1*-m AML compared with *NPM1* wild-type (*NPM1*-wt) AML (Issa et al, 2023). This demonstrates that any positive prognostic value associated with *NPM1*-m at diagnosis is lost in the R/R setting.

The FDA's Assessment:

The FDA agrees that the presence of an *NPM1* mutation at diagnosis is generally considered to be a favorable prognostic factor; however, the presence of *NPM1* mutation at the time of relapse does not confer a positive prognostic value. The review team agrees that up to 50% of patients with AML who achieve remission will later relapse, including those with an *NPM1* mutation.

The majority of mutations in the *NPM1* gene occur in exon 11 (previously thought to be exon 12) and result in cytoplasmic localization of the NPM1 protein, including the A, B, and D subtypes.¹ Co-mutations are often identified in analyses of *NPM1*m AML, including *FLT3*,

¹ Falini B, et al (2009). Altered nucleophosmin transport in acute myeloid leukaemia with mutated *NPM1*: molecular basis and clinical implications. *Leukemia*: 23;1731-43.

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IDH1/2, WT1, and DNMT3A, which may confound the prognostic implication of the *NPM1* mutation.²

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Therapeutic options are complex and largely rely on the patient's particular AML genomic subtype, age at diagnosis, overall performance status, access to standards of care, ability to tolerate the proposed treatment, and ultimate goals of therapy. Treatment of AML is initially divided into induction, consolidation, and postremission therapy. Hematopoietic stem cell transplant (HSCT) is currently the only potentially curative option for AML; however, HSCT is typically reserved for patients in remission who would clearly benefit from it as it is accompanied by a distinct set of life-threatening risks and complications (eg, graft-versus-host disease and higher nonrelapse mortality).

With the goal of eradicating leukemic cells to achieve CR, induction therapy with intensive chemotherapy is the standard of care for newly diagnosed AML patients able to tolerate the treatment intensity. In the US, the standard induction chemotherapy (ie, "7+3") consists of the combination of continuously infused cytarabine and intermittent dosing of an anthracycline administered over 7 and 3 days, respectively, and has remained the standard of care for decades. The combination regimen of venetoclax and azacitidine has received Food and Drug Administration (FDA) approval for the treatment of patients with newly diagnosed AML who are ineligible or unfit for standard induction therapy (eg, age and coexisting conditions). Other treatment options for patients in this category include lower doses of chemotherapy, targeted agents, or hypomethylating agents.

For consolidation or postremission therapy, treatment consists of HSCT; additional chemotherapy; and/or targeted therapies, such as FLT3, IDH1, and IDH2 inhibitors, for specific forms of AML. Per 2023 National Comprehensive Cancer Network (NCCN) guidelines in the R/R setting, clinical studies are strongly recommended as a treatment option before cycling through previously used available therapies (Pollyea et al, 2023).

Untreated AML is universally fatal. Currently, there are no FDA-approved or NCCN-recommended standard of care treatments for R/R *NPM1*-m AML and no therapies that target the underlying disease driver. Despite recent advances in the management of patients with AML, including the development of targeted and immune therapies and improvements in supportive care, the OS outcomes for patients with AML remain poor. Considering that *NPM1*-m AML represents approximately 30% of AML cases and leads to progressive deterioration in addition to

² Othman, J, et al (2024). Molecular, clinical, and therapeutic determinants of outcome in *NPM1*-mutated AML. Blood: 144;714-28.

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decreased lengths of survival in the R/R setting, a high unmet medical need exists in this population.

The FDA's Assessment:

The FDA agrees that at the time of the submission of the marketing application, there was no therapy approved for patients with R/R *NPM1*-m AML that specifically targeted this mutational pathway. For patients unable to tolerate intensive reinduction chemotherapy, options include lower intensity chemotherapy, including a hypomethylating agent with or without venetoclax. In addition, other targeted agents are approved for patients with coexisting mutations, such as *FLT3*-m (gilteritinib), *IDH1*-m (ivosidenib and olutasidenib), and *IDH2*-m (enasidenib) (FDA Table 1).^{2,3} Of note, only gilteritinib has shown a long-term survival benefit for patients with R/R AML in a randomized study.⁴

Prior to the PDUFA date for this application, the FDA approved revumenib, a menin inhibitor, for adult and pediatric patients with relapsed or refractory acute myeloid leukemia with a susceptible *NPM1* mutation who have no satisfactory alternative treatment options. However, the review team concurs that there remains a high unmet medical need for patients with R/R *NPM1*-m AML.

FDA Table 1. Approved targeted therapies for R/R AML and R/R acute leukemia

Response Rate	Gilteritinib: R/R <i>FLT3</i> -m AML N = 247	Ivosidenib: R/R <i>IDH1</i> -m AML N = 174	Enasidenib: R/R <i>IDH2</i> -m AML N = 199	Olutasidenib: R/R <i>IDH1</i> -m AML N = 147	Revumenib: R/R <i>KMT2A</i> -r acute leukemia N = 104	Revumenib: R/R <i>NPM1</i> -m AML N = 65
CR (95% CI)	14.2% (6.8, 18.1)	24.7% (18.5, 31.8)	19% (13, 25)	32% (25, 40)	12.5% (6.8, 20.4)	18.5% (9.9, 30)
CR + CRh (95% CI)	22.6% (17.5, 28.4)	32.7% (25.8, 40.3)	23% (18, 30)	35% (27, 43)	21.2% (13.8, 30.3)	23.1% (13.5, 35.2)
DoCR/CRh - median (95% CI)	7.4 months (<0.1, 23.1)	8.2 months (5.6, 12)	8.2 months (4.3, 19.4)	25.9 months (13.5, NR)	6.4 months (2.7, NE)	4.5 months (1.2, 8.1)

³ Issa GC, et al (2023). Clinical outcomes associated with *NPM1* mutations in patients with relapsed or refractory AML. *Blood Adv*: 793-42.

⁴ Perl AE, et al (2019). Gilteritinib or chemotherapy for relapsed or refractory *FLT3*-mutated AML. *New Engl J Med*: 381: 1728-40.

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TI-56	68/197 (34.5%)	41/110 (37.3%)	53/157 (34%)	29/86 (34%)	12/83 (14%)	8/46 (17.4%)
Overall Survival	HR 0.64 vs chemo (95% CI 0.49, 0.83) p 0.0004					
<i>Source: FDA review based on the USPIs for the respective drugs</i>						

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Ziftomenib is not currently registered or approved in the United States or in any other part of the world.

The FDA's Assessment:

The FDA agrees that ziftomenib is not yet approved in the United States or any other part of the world.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

The development of ziftomenib was initiated under IND 142,028. Key interactions between the FDA and Sponsor are detailed in [Applicant Table 1](#).

Applicant Table 1: Applicant - Summary of Regulatory History

Date	Milestone and Details
01 MAR 2019	IND 142,028 for ziftomenib (KO-539) was opened in the U.S. for the treatment of hematological malignancies.
22 JUL 2019	Orphan drug designation was granted for ziftomenib for the treatment of acute myeloid leukemia (AML).
02 FEB 2021	Type B EOP1 teleconference to discuss the patient selection strategy and development pathway for ziftomenib.
28 NOV 2022	Type C Meeting teleconference to discuss the RP2D and Phase 2 study design.
14 AUG 2023	Fast Track designation was granted for ziftomenib for the treatment of patients with R/R AML with a <i>NPM1</i> mutation.
09 NOV 2023	Type C Meeting teleconference to discuss the nonclinical and clinical pharmacology packages.
12 MAR 2024	Type C CMC Guidance Meeting preliminary comments to discuss regulatory starting materials, registration drug substance process, specifications and proposed dissolution method.
18 APR 2024	Breakthrough Therapy designation was granted for ziftomenib for the treatment of adult patients with R/R AML with <i>NPM1</i> mutations.
08 MAY 2024	Type C Meeting Written Response Only (WRO) to discuss the safety analysis strategy and clinical content plan for the NDA.

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16 AUG 2024	Initial Pediatric Study Plan (iPSP) agreed.
22 AUG 2024	Type B preliminary comments to discuss the overall development program and primary analysis for the NDA.
21 OCT 2024	FDA Interdisciplinary Review Team (IRT) for Cardiac Safety Studies agreed that the retrospective concentration-QT analysis from KO-MEN-001 is an adequate alternative to a Thorough QT study.
02 DEC 2024	FDA Advice on dissolution methodology.
03 FEB 2025	Type B Pre-NDA Meeting teleconference to discuss the final NDA content.

The FDA's Assessment:

The FDA agrees that the above interactions are accurate. In addition, key points of the above and additional interactions are further described below:

- EOP1 meeting (2 Feb 2021): FDA recommended having all patients screened by a single and analytically validated locked test of mutation at a central lab and employing one test/method using the same analytically validated reagents and procedure at all testing sites. FDA advised the Sponsor that the acceptable primary endpoint in treatment of R/R AML without intent to cure is CR + CRh, a direct measure of clinical benefit for regulatory decision making. In addition, FDA requested justification of proposed null rate based on historical data. FDA did not object to analyzing the efficacy data independently for each disease expansion cohort or to aggregating safety information across cohorts to provide a larger safety dataset for a future NDA submission.
- Partial Clinical Hold (22 Nov 2021): New enrollment in Study KO-MEN-001 was paused following a fatal event of differentiation syndrome (DS) in an enrolled participant with a rearrangement. The partial hold was removed on 20 January 2022 with supplementation of the DS risk mitigation guidance for investigators.
- Partial Clinical Hold letter (18 May 2022): Conduct of the healthy volunteer study KO-MEN-006 was prohibited following designation of ziftomenib as an epigenetic-modifying agent. The partial hold was removed on 11 January 2023 following submission of the abbreviated CSR for KO-MEN-006.
- Type C meeting (28 Nov 2022): FDA agreed that 600 mg QD was a reasonable RP2D for ziftomenib monotherapy, prompting the initiation of Phase 2 evaluation in adult patients with R/R AML with *NPM1*-m. In addition, FDA asked for justification of ziftomenib as a palliative therapy, for which CRh is considered as a direct clinical benefit. Further development as monotherapy in patients with *KMT2A*-r acute leukemia was discontinued.

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- Type B preliminary comments (22 Aug 2024): FDA objected to decreasing the null rate from 12% to ^{(b) (4)} and objected to reducing the sample size of Phase 2 portion and pooling Phase 1 and 2 data to establish the primary efficacy evidence for a future NDA submission.
- Type B pre-NDA Meeting (3 Feb 2025): FDA generally agreed to the content plan of the original NDA, including the content and timing of the safety update. FDA agreed on the submission of subject-level data for local *NPM1*-m testing in the absence of central testing or the originally planned contemporaneous Premarket Approval application of the companion diagnostic due to the change in companion diagnostic partner from ^{(b) (4)}

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted inspections for Study KO-MEN-001 at Clinical Sites 105 and 112. The sites were chosen on the basis of enrollment of large numbers of participants, a high proportion of participants with response to treatment, and a high number of protocol deviations per participant. Following inspection, Site 105 was determined to be No Action Indicated (NAI), and Site 112 was determined to be Voluntary Action Indicated (VAI). The VAI observations were mainly attributed to reporting and record accuracies and were considered to have little impact on the evaluation of the primary efficacy results. Site 112 provided an acceptable response and corrective action plan.

The Applicant (Kura) was also audited; the final classification for the Applicant's inspection was NAI. OSI concluded that the study data submitted to the Agency were acceptable for review in support of the proposed indication.

4.2. Product Quality

Ziftomenib drug product (200 mg; KOMZIFTI) is presented as a white opaque size 00 ^{(b) (4)}® plus capsule, imprinted with "ZIF 200" in black ink, and supplied in a 90-count configuration. The drug substance load is ^{(b) (4)}% w/w of the formulation. The inactive ingredients include mannitol, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. No excipient exceeds the maximum daily intake (FDA Table 20), and there were no novel excipients. The Drug Product is supplied in bottles of 90 tablets, with an expiry of 30 months when stored at USP controlled room temperature.

During clinical development, the Applicant utilized the same formulation throughout the clinical development process; therefore, bridging to the to-be-marketed formulation is not necessary.

^{(b) (4)} The capsule forms ^{(b) (4)} strengths, including the to-be-marketed forms, were used in KO-MEN-001. A biowaiver was neither requested nor needed.

No outstanding safety issues were identified for the manufacturing process or from the facilities inspections. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment under 21 CFR 25.31(b). The Product Quality review team recommends Approval of the NDA [DARRTS Reference ID 5668147].

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4.3. Devices and Companion Diagnostic Issues

For the participants in Study KO-MEN-001, local testing was used to identify participants with *NPM1* gene mutations for study enrollment. Participants with *NPM1* mutations identified as Type A, B, or D caused by a 4-nucleotide insert in exon 11 that results in *NPM1* cytoplasmic localization were eligible for the study. In addition, participants with other *NPM1* mutations that were deemed reasonably likely to result in cytoplasmic localization were eligible to enroll on the study. FDA Table 2 below shows the testing methodologies used in Phase 1b and Phase 2 of KO-MEN-001 and the identified *NPM1* mutations. The most commonly identified subtype was Type A, and the most common testing methodology was next-generation sequencing (NGS). However, 50% of patients in the Phase 1b portion and 28% of participants in the Phase 2 portion of KO-MEN-001 had a mutation that was either non-ABD or not reported by the local assay. Of note, participants were required to have a diagnostic bone marrow or peripheral blood sample banked centrally for retrospective confirmation once a central assay had been developed; this testing has not yet been performed.

FDA Table 2. KO-MEN-001 *NPM1* mutation subtype by testing methodology

<i>NPM1</i> Mutation Subtype	NGS, N(%)	PCR + capillary electrophoresis, N(%)	Qualitative PCR, N(%)	RT-qPCR, N(%)	Total, N(%)
Phase 1b (n=20)					
A	6 (30)	0	0	2 (10)	8 (40)
B	0	0	0	0	0
D	2 (10)	0	0	0	2 (10)
Non-ABD	2 (10)	0	0	0	2 (10)
Not reported	1 (5)	5 (25)	1 (5)	1 (5)	8 (40)
All Phase 1b	11 (55)	5 (25)	1 (5)	3 (15)	20 (100)
Phase 2b (n=92)					
A	34 (37)	9 (10)	1 (1)	8 (9)	52 (57)
B	2 (2)	2 (2)	1 (1)	0	5 (5)
D	7 (8)	1 (1)	1 (1)	1 (1)	10 (11)
non-ABD	4 (4)	2 (2)	0	0	6 (7)
Not reported	3 (3)	12 (13)	0	4 (4)	19 (21)
All Phase 2	50 (54)	26 (28)	3 (3)	13 (14)	92 (100)
<i>Source: CDTL Analysis. NPM1P1B.xpt, NPM1P2.xpt</i>					

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While the majority of clinically detected mutations in *NPM1* result in cytoplasmic localization of the NPM1 protein, there are reports of mutations in exons other than exon 11 which retain nuclear localization.⁵ The review team notes that a significant proportion of participants enrolled on KO-MEN-001 had either unreported mutation subtype or non-ABD subtype. As such, the Division has determined that a companion diagnostic assay is needed to ensure safe use of ziftomenib, and the Applicant has committed to develop such an assay as a postmarketing commitment (see Section 13).

⁵ Sondka Z, et al (2024). COSMIC: a curated database of somatic variants and clinical data for cancer. *Nuc Acids Res*: 52: D1210-17. (www.cosmicb.org)

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5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The FDA's Assessment:

Ziftomenib is a menin inhibitor. Menin is a nuclear scaffold protein that is part of protein complexes that regulate gene transcription via chromatin remodeling. Menin binds directly to the N-terminal of mixed lineage leukemia lysine methyltransferase 2a (MLL [KMT2A]), and this interaction is involved in nucleophosmin 1(NPM1)-driven gene regulation. Ziftomenib binds to menin at the KMT2A binding site and disrupts the interaction between menin and KMT2A. The proposed indication for ziftomenib is for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible *NPM1* mutation. The leukemogenic activity of mutant NPM1 is mediated by the interactions between menin and MLL[KMT2A]. Susceptible *NPM1* mutations are defined as those that result in loss of the nucleolar localization signal and the insertion of a new nuclear export signal leading to the cytoplasmic accumulation of mutant NPM1 and leukemogenesis.

Ziftomenib inhibited the interaction between recombinant menin and a KMT2A peptide (IC₅₀ = 37 nM), suggesting that ziftomenib can inhibit the interaction between menin and KMT2A fusion proteins. Ziftomenib showed anti-proliferative activity against a variety of leukemia and lymphoma cell lines with different KMT2A fusion states (IC₅₀ = 3.9-31 nM). Alterations to menin-KMT2A target genes were also induced in these models. The in vivo anti-tumor activity of ziftomenib was evaluated in xenograft models using the human AML cell lines MV4-11 and MOLM-13 and patient-derived cells in immunocompromised rats and mice with oral administration and a variety of treatment durations. Overall, ziftomenib showed dose-dependent anti-tumor activity in these nonclinical in vivo models. These findings are supportive of the mechanism of action of ziftomenib as described in the label. In binding assays conducted to determine off-target binding, ziftomenib did not show high levels of activity against the targets evaluated under the conditions tested, suggesting a low potential for off-target activity in a physiologically relevant context.

Based on findings from non-GLP and GLP assays, ziftomenib has the potential to block the human Ether-a-go-go-Related Gene (hERG) and the human L-type voltage-dependent calcium channel, alpha 1C subunit (hCav1.2) channels. The IC₅₀ values for hERG and hCav1.2 inhibition were 1.61 and 2.8 μM, respectively. Dose-dependent lower blood pressure and longer PR intervals were seen after single doses of 40, 120, and 200 mg/kg/day in dogs, while decreases in heart rate, and increases in RR interval were noted at 200 mg/kg/day during a 13-week repeat-dose study in dogs.

The bioavailability of ziftomenib ranged from 11.4% in monkeys to 35% in dogs. Ziftomenib

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distribution in the mouse was the highest in the small intestine, stomach wall, cecum, liver, gall bladder, eye (uveal tract), kidneys, spleen, and Harderian gland at concentrations that were sustained to 672 hours post-dose. Ziftomenib showed plasma protein binding of greater than 95% across species and human plasma protein type. In repeat-dose toxicology studies in mice and dogs, exposure (area under the curve or C_{max}) generally increased with increasing dose in a less than dose proportional manner in 28-day studies and a greater than dose proportional manner in 13-week studies. In vitro studies did not identify unique or major human metabolites.

The GLP-compliant repeat-dose toxicology studies with up to 13 weeks of dosing were conducted in mice and dogs with animals dosed twice daily via oral gavage. In the 4-week mouse study, animals received ziftomenib at doses of 40, 120, or 400 mg/kg/day. The high dose was poorly tolerated, with unscheduled deaths leading to a dosing holiday and a dose reduction to 200 mg/kg/day. Clinical signs included severe dehydration, decreased activity, and pale skin. Gross pathology revealed green discoloration in the liver in mid- and high-dose group animals, which correlated with increased transaminase and bilirubin levels, increased liver weight, and macrophage infiltration, demonstrating liver toxicity. Microscopic findings of cellular infiltration and vacuolation were observed in the lung and lymphoid tissues. A decrease in erythrocyte counts was also observed with associated decreases in hematocrit and hemoglobin.

In the 13-week mouse study, animals were given ziftomenib at doses of 12, 40, or 120 mg/kg/day. Unscheduled deaths occurred in all dosing groups. While the cause of death was not determined for most of these incidences, the death of a mid-dose group female is notable due to the malignant lymphoma found in the lymph nodes, thymus, bone marrow, heart, kidney, liver, lung, ovary, spleen, and stomach. Malignant lymphoma was determined to be the cause of morbidity. The average exposure to animals at 40 mg/kg/day was approximately 2 times the exposure in patients receiving the recommended dose of ziftomenib. Given the incidences of hyperplasia observed with the drug, it is reasonable to conclude that ziftomenib may be responsible, and the finding has been added to the label. Notable findings for the surviving animals included reversible basophil, large unstained cell, monocyte, and neutrophil count increases, irreversible elevated liver enzymes, and increased adrenal gland, pituitary gland, kidney, liver, spleen, and thymus weights in the high-dose groups. Microscopic findings in the liver included pigmentation in high-dose groups and dose-dependent hypertrophy among males and high-dose females. Dose-dependent hyperplasia was observed in the adrenal glands in males and high-dose females. Ziftomenib exposures at the high dose in mice (AUC = 61500 ng*hr/mL) were approximately 5 times the human exposure (AUC = 12200 ng*hr/mL) at the recommended dose of 600 mg once daily.

In the 4-week dog study, ziftomenib was administered at doses of 20, 60, or 200 mg/kg/day. Two unscheduled deaths occurred in high-dose group males that were likely due to severe alveolar edema and hemorrhage. Surviving mid-dose and high-dose animals showed clinical findings of dehydration, abnormal feces, and vomitus that correlated with gastrointestinal tract toxicity noted

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upon gross pathologic and microscopic examination. Findings of elevated protein in the urine correlated with findings of tubular degeneration and membranous glomerulopathy in the kidneys. Other target organs included the liver and the thymus, where white blood cell infiltration, vacuolation, and lymphoid depletion was noted microscopically. The microscopic findings persisted at the end of the recovery period.

In the 13-week toxicology study in dogs, animals were given ziftomenib at doses of 6, 20, or 60 mg/kg/day. While all animals survived to the scheduled necropsies, clinical findings included reversible reduced activity, hunched posture, wet fur, salivation, and thin appearance in the high-dose group animals. Electrocardiogram readings identified a decrease in heart rate that correlated with increased RR intervals. The liver was the primary organ of toxicity, where elevated liver enzyme levels in the blood were observed along with discoloring and microscopic findings of cholestasis and biliary hyperplasia. Other organs of toxicity included the lymph node, spleen, gall bladder, thymus, ovaries, bone marrow, adrenal glands, parathyroid gland (females), pituitary gland, and epididymis (reduced sperm). A high-dose group female had findings of hyperplasia in several tissues, including the liver, pancreas, thymus, heart, aorta, adrenal glands, and mammary glands. The observance of hyperplasia in both mice and dogs is being added to Section 13.2 of the label. Ziftomenib exposures at the high dose in dogs (AUC = 18700 ng*hr/mL) were approximately 1.5 times the human exposure (12200 ng*hr/mL) at the recommended dose of 600 mg once daily. Clinical adverse events noted in the label include infection, differentiation syndrome, febrile neutropenia, pyrexia, electrocardiogram QT prolongation, bacterial infection, leukocytosis, cardiac failure, cholecystitis, diarrhea, and pruritus. There is overlap between the toxicology profile in the dog, with the immune and cardiac systems as affected areas, and the noted clinical observations.

In the pivotal embryo-fetal development study, pregnant mice received ziftomenib doses of 6, 20, or 60 mg/kg/day during organogenesis from gestational day 6 to gestational day 15. Maternal body weight and weight gains were lower in the high-dose animals by the end of the dosing period and continued to the end of the recovery period. Post-implantation loss was higher in the high-dose group due to a higher number of dead fetuses, which in turn was due to 1 high-dose group animal that had a litter entirely composed of dead fetuses. Mean fetal weights were modestly lower in all test article groups. External malformations were elevated in the high-dose group fetuses and composed of cleft palates. Skeletal malformations were observed in all test article dose groups, notably in the ribs, skull, and vertebra. Exposures at the lowest dose were approximately 0.3 times the human exposure (AUC) at the recommended clinical dose of 600 mg once daily. Based on data from the embryo-fetal development study and ziftomenib's mechanism of action, a warning for embryo-fetal toxicity is included in the labeling for this product. The 13-week toxicity study in dogs showed changes to male and female reproductive organs that included decreased testis weight, increased vacuolation of the seminiferous tubular epithelial cells, a marked decrease in sperm in the epididymal lumen, and fewer developing follicles in the ovaries. At the dose of 60 mg/kg/day, with exposures as low as 1.2 times the

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human exposure, the findings were not reversible after the 4-week recovery period. While ziftomenib showed no genotoxic potential in standard genetic toxicology studies, based on its activity as an epigenetic modifier and the reproductive findings in the 13-week toxicology studies, the FDA proposes a 3-month duration of continued contraception for males and a 6-month duration for females after the last administration of ziftomenib, consistent with the recommendations for genotoxic drugs.

The nonclinical data submitted with this NDA support approval of ziftomenib for the proposed indication from a Pharmacology/Toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for ziftomenib.

The FDA's Assessment:

The FDA agrees with this statement.

5.3. Pharmacology

Primary Pharmacology

The Applicant's Position:

In vitro studies demonstrated that ziftomenib inhibited binding of an MLL(KMT2A)-derived peptide to menin in a cell-free biochemical assay with an IC₅₀ of 37 nM (Study KO-PD-0015) and inhibited cell proliferation with IC₅₀ values ranging from 4 to 31 nM in a panel of 6 KMT2A-r cell lines (Study KO-PD-0016). Ziftomenib showed no activity, with IC₅₀ values $\geq$ 1800 nM, in 4 menin-independent AML cell lines. Ziftomenib induced apoptosis in KMT2A-r cell lines in a time- and concentration-dependent manner, peaking at around 80% in MV4;11 cells and 60% in KOPN8 cells after 7 days of treatment (Study KO-PD-0017). Ziftomenib drove changes in menin-dependent gene expression that were detectable within 2 to 4 days and that increased up to Day 7 (Study KO-PD-0018) including inhibiting expression of HOXA9 and MEIS1 with IC₅₀ values around 10 nM and 50 nM cells after 4 days of treatment in the KMT2A-r cell lines MV4;11 and KOPN8, respectively; inhibiting expression of MEIS1 with an IC₅₀ of 6.6 nM in the KMT2A-wt, NPM1/DNMT3A-mutant cell line OCI-AML3 and inducing expression of the differentiation marker CD11b in all 3 cell lines with an IC₅₀ of approximately 50 nM.

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In vitro evaluation of the metabolite KO-516 and metabolite KO-739

KO-516 and KO-739 are pharmacologically active metabolites and were identified in mouse and dog plasma as main metabolites. They are also present in human plasma as minor metabolites.

KO-516 inhibited binding of an MLL(KMT2A)-derived peptide to menin in a cell-free biochemical assay with an IC₅₀ of 27 ± 13 nM (Study KO-PD-0015) and inhibited cell proliferation with IC₅₀ values ranging from 4 to 24 nM for 4 *KMT2A*-r cell lines (Study KO-PD-0016).

KO-739 inhibited menin-MLL(KMT2A) peptide interactions with IC₅₀ values of 48.56 nM and 52.50 nM for 2 separate batches of menin (Study KO-PD-0201) and inhibited cell proliferation with an IC₅₀ value of 44.1 ± 14.8 nM in the *KMT2A*-r cell line MV4;11 (Study KO-PD-0200).

In Vivo Cell Line-Derived Xenograft (CDX) Models

SC and disseminated MV4;11 CDX rodent models of *KMT2A*-r AML:

- In the disseminated MV4;11 mouse model, ziftomenib induced stasis at 50 mg/kg/day and regression at 100 mg/kg/day following once daily (QD) treatment for 6 days (Study KO-PD-0019). Therapeutic activity was accompanied by dose-dependent downregulation of the menin-MLL(KMT2A) target genes *HOXA9* (~2-fold) and *MEIS1* (almost 50-fold) as well as induction of *CD11b* (~25-fold) in bone marrow.
- In the SC MV4;11 mouse model, ziftomenib at 50 or 100 mg/kg/day reduced tumor burden to undetectable levels within 2 to 4 weeks following QD oral (PO) administration (Study KO-PD-0020). All ziftomenib-treated animals remained tumor free following a 33-day post-treatment observation period.
- In the disseminated MV4;11 mouse model, ziftomenib at 100 mg/kg/day reduced circulating blasts to trace levels within 16 days of the 3-week dosing period (Study KO-PD-0021). Mice treated at 50 or 100 mg/kg/day ziftomenib survived at least 24 days longer than controls although all animals eventually succumbed.
- In the SC MV4;11 nude rat model, ziftomenib at 30 or 100 mg/kg/day for 28 days led to 100% tumor growth inhibition (TGI) in all animals (Study KO-PD-0024).

Hyper-aggressive disseminated MOLM13 CDX mouse model of *KMT2A*-r AML:

- Ziftomenib dosed at 100 mg/kg/day QD for 29 days prevented leukemia progression during the dosing period (Study KO-PD-0022). Animals relapsed in a dose-dependent fashion, with median survival prolonged from 17 days in the vehicle group to 20, 26, and 48 days in mice treated with ziftomenib at 25, 50, and 100 mg/kg/day, respectively.
- When ziftomenib was tested in comparison to and in combination with the standard-of-care treatments azacitidine and venetoclax, ziftomenib at 100 mg/kg/day QD for 42 days beginning 3 days post-transplantation prolonged median survival time beyond the 96-day

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duration of the experiment as compared to 21, 26, and 33 days in vehicle-treated, venetoclax-treated, and venetoclax/azacitidine-treated animals, respectively (Study KO-PD-0027). All 8 animals treated with ziftomenib/venetoclax/azacitidine remained healthy at the end of the experiment, whereas 3 of 8 ziftomenib-treated and 5 of 8 ziftomenib/venetoclax-treated animals succumbed to AML

In Vivo Patient-Derived Xenograft (PDX) Models

Disseminated PDX mouse model of KMT2A-r AML bearing an MLL(KMT2A)-P300 rearrangement (Study KO-PD-0023):

- Ziftomenib at 100 mg/kg/day QD for 21 days beginning 18 days post-transplantation reduced tumor burden in spleen, peripheral blood, and bone marrow to negligible levels (<0.1% of all cells) at the end of a 125-day follow-up period as compared to levels of approximately 20% in the controls. All ziftomenib-treated mice survived to the end of the 125-day follow-up period as compared to a median survival of 42 days in the control animals.

Disseminated AM7577 NPM1/DNMT3A/IDH2/FLT3-mutant PDX mouse model of KMT2A-wt AML in comparison to and in combination with the FMS-like tyrosine kinase 3 (FLT3)-inhibitor quizartinib (AC220) (Study KO-PD-0025):

- Ziftomenib at 100 or 150 mg/kg/day alone or at 100 mg/kg/day in combination with AC220 at 2 mg/kg/day administered QD for 6 weeks resulted in no detectable human leukemic blasts at sacrifice whereas all vehicle-treated and most AC220-treated animals were inundated with blasts at sacrifice. No animals treated with ziftomenib, alone or in combination with AC220, succumbed to leukemia-related disease during the 100-day experiment, while AC220 as a single agent prolonged survival of tumor-bearing mice by 193% relative to controls

Ziftomenib tested with several intermittent dosing schedules that introduced dosing holidays after 1, 2, or 3 weeks of treatment in the disseminated AM7577 NPM1/DNMT3A/IDH2/FLT3-mutant PDX mouse model of KMT2A-wt AML (Study KO-PD-0205) showed that

- Ziftomenib at 50 mg/kg/day for Weeks 1 to 8 or at 100 mg/kg/day for Weeks 1 to 8; Weeks 1 to 3 and 4 to 7; Weeks 1 to 2 and 4 to 6; or Weeks 1, 3, 5, and 7 reduced circulating blast counts below detectable levels within 28 days of the 56-day dosing period
- All ziftomenib-treated animals survived and remained tumor free at the end of the experiment (following a further 8-week observation period) with the exception of 2 mice treated with the 1-week-on/1-week-off regimen
- The minimum fully efficacious dose of ziftomenib on a continuous schedule in this model was 50 mg/kg QD, and the minimum fully efficacious continuous dosing period was 2 weeks.

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In vivo evaluation of antitumor activity of ziftomenib tested in comparison to AC220 in the LEXFAM 2734 NPM1/IDH1/FLT3-mutant PDX model of KMT2A-wt AML in NOG mice (Study KO-PD-0026) found that

- Ziftomenib at 150 mg/kg/day QD for 61 days resulted in reduced tumor load at termination to 0.44% of peripheral blood cells as compared to 45.7% and 61.6% for AC220- and vehicle-treated animals, respectively.
- Tumor load at termination in bone marrow was 18.8%, 53.2%, and 31.6% of cells for ziftomenib-, AC220-, and vehicle-treated groups, respectively, with 4 of 5 ziftomenib-treated animals exhibiting almost undetectable levels of tumor cells.
- Human cells in the ziftomenib-treated mice showed clear evidence of myeloid differentiation, with 77.3% of human cells expressing CD11b at Day 35

Ziftomenib-treated animals had 60% survival at Day 76 as compared to 0% survival by Day 76 in the AC220-treated animals and 0% survival by Day 37 in control animals.

The FDA's Assessment:

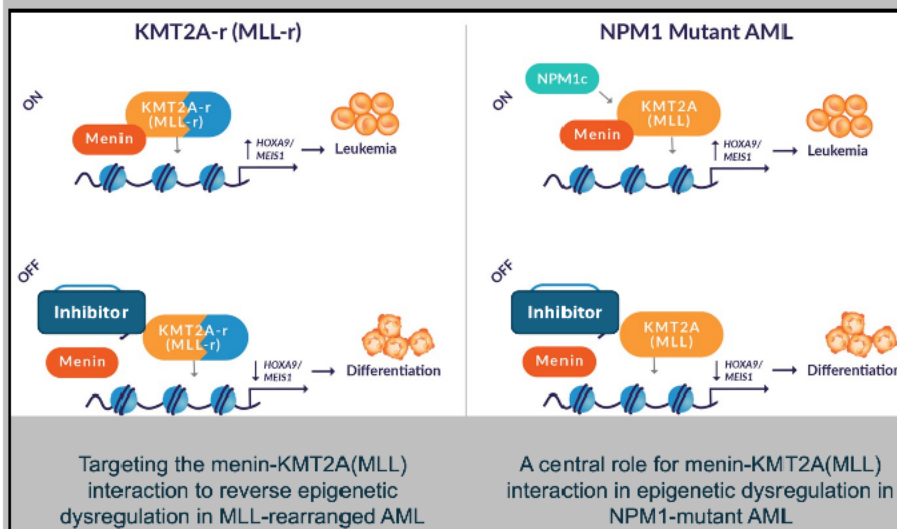
The FDA concurs with the Applicant's assessment for the primary pharmacology of ziftomenib. By disrupting the interactions between menin and KMT2A (wild-type or rearranged), menin inhibitors disrupt the leukemogenic transcriptional signaling induced by chromatin-binding complexes that are facilitated by and contain menin and rearranged KMT2A. NPM1 is a multifunctional protein that typically resides in the nucleolus but becomes mainly cytosolic and a leukemogenic driver when it is mutated (NPM1c). The leukemogenic activity of NPM1c is mediated by the activity of the menin/KMT2A (wild-type or rearranged) chromatin-modulating complex and is inhibited by the activity of menin inhibitors.

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FDA Figure 1. Summary of the Role Menin Inhibitors Play in Mitigating NPM1/KMT2A-Induced Leukemogenesis⁶



In vitro and in vivo studies that demonstrate ziftomenib’s mechanism of action, anti-proliferative activity, and anti-tumor activity are summarized in the following tables:

FDA Table 3. Summary of In Vitro Primary Pharmacology Studies with Ziftomenib

Study #	Model	Concentrations	Treatment time	Readout	Findings
KO-PD-0015	Menin/ MLL(KMT2A)-derived peptide binding inhibition	1 nM – 10 µM	1 hour	Fluorescence polarization change	Ziftomenib IC50 = 37 nM KO-516 (metabolite) IC50 = 27 nM
KO-PD-0016	10 leukemia and lymphoma cell lines	1 nM – 10 µM	7 days	% Proliferation inhibition	Ziftomenib IC50s: 3.9 – 31 nM KO-516 IC50s: 4.2 – 24 nM

⁶ Adapted from Goldberg AD, Corum D, Ahsan J, et al. Komet-008: A Phase 1 Study to Determine the Safety and Tolerability of Ziftomenib Combinations for the Treatment of KMT2A-Rearranged or NPM1-Mutant Relapsed/Refractory Acute Myeloid Leukemia. Blood 2023; 142 (Supplement 1): 1553. doi: <https://doi.org/10.1182/blood-2023-190475>

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Study #	Model	Concentrations	Treatment time	Readout	Findings
KO-PD-0017	MV4;11 and KOPN8 cell lines	1 nM – 300 nM	2 – 7 days	Apoptosis (% sub-G1 DNA)	Concentration- and time-dependent apoptosis
KO-PD-0018	MV4;11, KOPN8, and OCI-AML3 cell lines	0.1 nM - 300 nM	2 - 7 days	Change in biomarker mRNA expression	↓ HOXA9 and MEIS 1 ↑ CD11b
KO-PD-0200	MV4;11 and U937 cell lines	0.5 nM – 10 μM	6 days	% Proliferation inhibition	KO-739 (metabolite) IC50: 44.1 nM
KO-PD-0201	Menin/ MLL(KMT2A)-derived peptide binding inhibition	0.17 nM – 10 μM	1 hour	Fluorescence polarization change	KO-739 IC50: 48.6-52.5 nM

FDA Table 4. Summary of In Vivo Primary Pharmacology Studies with Ziftomenib

Study #	Species/strain	AML model	Route of dosing	Dose	Dosing duration	Result summary
KO-PD-0019	Non-obese diabetic (NOD) severe combined immunodeficient (SCID) gamma (NSG) mice	MV4-11-luc cell line intravenous	Oral	25, 50, or 100 mg/kg daily	6 days	↓ tumor burden, target gene modulation
KO-PD-0020	Nude mice	MV4-11 cell line subcutaneous	Oral	50 or 100 mg/kg daily	3 weeks	↓ tumor volume
KO-PD-0021	NSG mice	MV4-11-luc cell line intravenous	Oral	50 mg/kg 2x/day, 100 mg/kg/day	10 days	↑ life span
KO-PD-0022	NSG mice	MOLM13 cell line intravenous	Oral	25, 50, or 100 mg/kg/day	29 days	↓ tumor burden, ↑ life span
KO-PD-0023	NOD SCID IL3Rγ, GM-CSF, SCF triple transgenic (SGM3) (NSGS) mice	Patient-derived AML cells (PDX) intravenous	Oral	100 mg/kg/day	20 days	↓ tumor burden, ↑ life span

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Study #	Species/strain	AML model	Route of dosing	Dose	Dosing duration	Result summary
KO-PD-0024	Nude rats	MV4-11 cells subcutaneous	Oral	10, 30, or 100 mg/kg/day	28 days	↓tumor volume
KO-PD-0025	NOD/SCID mice	AML7577 cells intravenous	Oral	100 or 150 mg/kg/day	6 weeks	↓tumor burden, ↑life span
KO-PD-0026	NOD/IL-2R γ (NOG) Mice	Patient-derived AML cells (PDX) intratibial	Oral	150 mg/kg/day	61 days	↓tumor burden, ↑life span
KO-PD-0027	NOD/SCID Mice	MOLM13 cell line intravenous	Oral	100 or 200 mg/kg/day	42 days	↑survival
KO-PD-0205	NOD/SCID mice	AML7577 cells intravenous	Oral	50 or 100 mg/kg/day	≤8 weeks	↓tumor burden, ↑life span

Secondary Pharmacology

The Applicant's Position:

The selectivity of ziftomenib (10 μ M) was evaluated in a radioligand binding assay against a panel of 55 purified receptors, ion channels, and transporters. In this assay, > 50% inhibition of ligand binding to the human 5-HT_{2B} receptor was observed in the presence of 10 μ M ziftomenib (KO-PD-0028). Subsequently, an IC₅₀ value of 10 μ M against the human 5-HT_{2B} receptor (an antagonist effect) was determined from concentration-response curves in a cell-based functional assay (KO-PD-0029). Given that ziftomenib is highly plasma protein bound, the observed off-target in vitro inhibitory activity against the human 5-HT_{2B} receptor at 10 μ M is considered unlikely to be clinically relevant in humans.

The FDA's Assessment:

The FDA generally agrees with the statements above. Ziftomenib (FAA-02) at 10 μ M was used to screen a panel of 55 receptors, ion channels, and transporters for activity modulation. Ziftomenib decreased activity of the 5-hydroxytryptamine 2B (5-HT_{2B}) receptor by 96%, by 39% for the C-C chemokine receptor type 1 (CCR1) and by 24% for the neuropeptide Y receptor type 1 (Y1, study KO-PD-0028). In another study (study KO-PD-0029), the IC₅₀ for ziftomenib inhibition of the 5-HT_{2B} receptor was determined to be 10 μ M.

Safety Pharmacology

The Applicant's Position:

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In a multiple ion channel assay, IC₅₀ values calculated for ziftomenib at channels containing the hERG, hCav1.2, or hNav1.5 were 1.583, 2.797, and > 50 μM (estimated at 142.489 μM), respectively (Study KO-TOX-0021). Logistic regression modeling identified a low torsadogenic risk for ziftomenib due to comparable hERG and hCav1.2 potencies.

In the GLP-compliant hERG assay, ziftomenib inhibited hERG current by (mean ± standard error of the mean) 70.8 ± 2.5% at 0.066 μM (0.048 μg/mL) and 95.0 ± 0.7% at 1.62 μM (1.17 μg/mL) versus 11.1 ± 2.6% in the vehicle control group. hERG inhibition at 0.066 μM and 1.62 μM was statistically significant (p < 0.05) when compared to the vehicle control value. The IC₅₀ for the inhibitory effect of ziftomenib on hERG potassium current was considered to be less than 0.066 μM (0.048 μg/mL), the lowest concentration evaluated (Study KO-TOX-0023).

In the GLP-compliant cardiovascular study in telemetered dogs (n=4/group) single PO doses of 0 (vehicle: (b) (4) ® in reverse osmosis deionized water with 3.0 molar equivalent (b) (4) pH (b) (4) 40, 120, or 200 mg/kg were administered (Study KO-TOX-0022). While test article-related effects on hemodynamic parameters (decreased systolic and mean arterial pressures) and PR interval duration (prolongation) were noted between 6 and 24 hours postdose, no evidence of arrhythmogenic potential (ie, no ziftomenib-related effects on the QRS complex, RR, QT, or heart rate corrected QT (QTc) interval durations and no ziftomenib-related changes in electrocardiogram (ECG) waveform morphology).

The FDA's Assessment:

The FDA generally agrees with the Applicant's statements. Ziftomenib activity on the hCav1.2, hERG, and hNav1.5 ion channels was evaluated at concentrations of 0.5, 3, 10, and 50 μM by the patch clamp method when the genes were expressed in HEK293 or CHO cells (study KO-TOX-0021). The resulting IC₅₀ values were 1.6 μM for hERG and 2.8 μM for hCav1.2, but the IC₅₀ could not be determined for hNav1.5 because it was higher than the highest dose used. In a GLP study with the hERG channel (study KO-TOX-0023), ziftomenib at 66 nM and 1.62 μM inhibited at 71% and 95%, respectively. The IC₅₀ value could not be calculated but was determined to be less than 66 nM.

Telemetered dogs were used to determine the effects of single oral ziftomenib doses (40, 120, and 200 mg/kg; study KO-TOX-0022) on heart rate, arterial blood pressure, pulse pressure, body temperature, and electrocardiogram activity (PR, QRS, QT, and QTc; study KO-TOX-0022). Observations were recorded over 24 hours. Notable observations occurred between 6 and 24 hours after dosing and included dose-dependent lower blood pressure and longer PR intervals. The observations were no more than 10% different from control levels. Cardiovascular assessments were made during the 28-day and 13-week GLP repeat-dose toxicology studies in dogs. While there were no notable observations attributed to ziftomenib in the 13-week study, heart rate decreases resulting from increases in the RR interval were observed in the high-dose animals (200 mg/kg/day) during the 28-day study.

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5.4. ADME/PK

The Applicant's Position:

Absorption
In Vitro
Ziftomenib had moderate permeability in human colorectal adenocarcinoma (Caco-2) cell monolayers (Study KO-ADME-0037). Ziftomenib transporter substrate studies (Studies KO-ADME-0038, KO-ADME-0200): Transporter substrate assessments demonstrated that ziftomenib was a breast cancer resistance protein (BCRP) substrate and a P-glycoprotein (P-gp) substrate in Madin-Darby canine kidney II (MDCKII) cells. Ziftomenib was not a bile salt export pump (BSEP) or multidrug resistance-associated protein 2 (MRP2) substrate. Transporter inhibition studies (Study KO-ADME-0038): Transporter inhibition assessments demonstrated that ziftomenib was not an inhibitor of BCRP, organic anion transporter (OAT)1, OAT3, organic anion transporting polypeptide (OCT)2, or multidrug and toxin extrusion transporter (MATE)2-K under the conditions of this study, and ziftomenib had no meaningful inhibitory effect on the remaining transporters tested as follows: Ziftomenib was not an inhibitor of P-gp (inhibited no more than 29.0% of uptake at 5 µM, the highest concentration tested), organic anion transporting polypeptide (OATP) 1B1 (inhibited no more than 18.8% of uptake at 5 µM, the highest concentration tested), or OATP1B3 (inhibited no more than 13.1% of uptake at 5 µM, the highest concentration tested), as the inhibition was less than 50%. Ziftomenib was not an inhibitor of BSEP, MRP2, and MATE1-mediated uptake at the highest concentrations tested, as inhibition was less than 5%.
In Vivo
Single-Dose Pharmacokinetics across species of an Intravenous Bolus or Oral Dose of ziftomenib (Studies KO-ADME-0032, KO-ADME-0033, KO-ADME-0034, KO-ADME-0035) Orally administered 10 mg/kg, ziftomenib was rapidly absorbed in female mice (time to maximum concentration [t_{max}] of 1.0 h), rats (4.7 h), dogs (2.7 h), and monkeys (4.0 h). The oral bioavailability of ziftomenib was 34% in BALB/c mice, 24% in Sprague Dawley rats, 35% in beagle dogs, and 11% in cynomolgus monkeys. Plasma clearance (CL) was low in mice and moderate in rats, dogs, and monkeys. The volume of distribution at steady state (V_{ss}) was low in mice and high in rats, dogs, and monkeys. The elimination half-life (t_{1/2}) was 3.5 h in mice, 10 h in rats, 11.6 h in dogs and 9.1 h in monkeys. Toxicokinetics in GLP compliant 28 day and 13-week oral repeat dose toxicity studies in CD-1 mice (Studies KO-TOX-0009, KO-TOX-0010) and beagle dogs (Studies KO-TOX-0012, KO-TOX-0013)

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Ziftomenib displayed TK profiles at steady state that increased with dose and were of varying dose-proportionality after repeated oral administration. There were no sex differences in exposure at any dose level in either species, and no meaningful accumulation of ziftomenib was observed after repeated dosing for 13 weeks.
Distribution
In Vitro
In Vitro Determination of Protein Binding of KO-539 in CD-1 Mouse, Sprague Dawley Rat, Beagle Dog, Cynomolgus Monkey, and Human Plasma / Study KO-ADME-0042 / Section 4.1.2 of Module 2.6.4, Section 7 of Module 2.6.5.
Ziftomenib (5, 10, and 15 µM) exhibited high binding to plasma proteins that was independent of concentration, and there was no marked difference in plasma protein binding across species (>99% in mouse, rat, dog, monkey, and human; using equilibrium dialysis).
Protein Binding Study of KO-539 in Human Plasma Components by Ultracentrifugation / Study KO-ADME-0045 / Section 4.1.3 of Module 2.6.4, Section 7 of Module 2.6.5
Ziftomenib (2 and 10 µM) was highly bound (>95%) to all tested protein components of human plasma (≥99.5% for human serum albumin, ≥98.9 for low-density lipoproteins, ≥98.0% for high-density lipoproteins, ≥95.5% for α1-acid glycoprotein, and ≥95.8% for γ-globulins; using ultracentrifugation).
In Vitro Assessment of KO-539 of Protein Binding in Human Liver Microsomes / Study KO-ADME-0046 / Section 4.1.4 of Module 2.6.4, Section 9 of Module 2.6.5
Ziftomenib (0.015, 0.045, 0.09, 0.15, 0.45, 0.9, 1.5 and 4.5 µM) exhibited high binding to human liver microsome proteins using rapid equilibrium dialysis that was independent of concentration (ranging from 94.6% to 99.8%).
Determination of In Vitro Blood to Plasma Ratio (B:P) of KO-539 in CD-1 Mouse, SD Rat, Beagle Dog, and Human / Study KO-ADME-0046 / Section 4.1.1 of Module 2.6.4, Section 9 of Module 2.6.5
Ziftomenib (0.1, 1.0, and 10 µM) demonstrated low partitioning into red blood cells across species. The blood-to-plasma ratio ranged from approximately 0.6 to 0.72 in the mouse, 0.78 to 1.16 in the rat, 0.61 to 0.64 in the dog and 0.60 to 0.73 in humans. No significant concentration-dependent partitioning was observed in any species.
In Vivo
Plasma and Brain Exposure of KO-539 in Female CD-1 Mice Following a Single Oral Dose / Study KO-ADME-0041 / Section 4.2.2 of Module 2.6.4, Section 6 of Module 2.6.5
The ziftomenib exposure ratio of brain/plasma after a single 50 mg/kg oral dose of ziftomenib in female CD-1 mice (n=3 per timepoint; 0.5, 1, 2, 4, 6, 8, and 24 h postdose) was 8.15%

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indicating ziftomenib displayed a low distribution and rapid equilibrium across the blood-brain barrier.
Pharmacokinetics, Distribution, Metabolism, and Excretion of 14C-KO-539 Following Oral Administration to Mice / Study KO-ADME-0044 / Section 4.2.1 of Module 2.6.4, Section 6 of Module 2.6.5 After single oral gavage administration of [¹⁴C]ziftomenib in BALB/c and C57BL/6 mice, radioactivity was distributed to tissues, with most tissues having reached C_{max} by 24 h post dose. Distribution trends were similar across pigmented and nonpigmented strains, except that radioactivity was distributed in the uveal tract, indicating binding to melanin-containing tissues with evidence of elimination of radioactivity from melanin containing tissues over time. Low levels of radioactivity were detected in the brain at 24 h, but these were the lowest C_{max} values observed of all tissues, indicating a low extent of [¹⁴C]ziftomenib-derived radioactivity crossing the blood-brain barrier. Low levels of radioactivity were measured in the testis, also indicating the low extent of [¹⁴C]ziftomenib-derived radioactivity crossed the blood-testis barrier.
Metabolism
In Vitro
Evaluation of the In Vitro Metabolic Stability of KO-539 Using Liver Microsomes of Various Mammalian Species / Study KO-ADME-0047 / Section 5.1.1.1 of Module 2.6.4, Section 10 of Module 2.6.5 Metabolite Profiling of Ziftomenib in Liver Microsomes Across Species / Study KO-ADME-0049 / Section 5.1.1.2 of Module 2.6.4, Section 10 of Module 2.6.5 The ziftomenib in vitro t_{1/2} values in mouse, rat, dog, monkey, and human liver microsomes were 22.9, 21.6, 55, 8.4, and 19.4 minutes, respectively. The short t_{1/2} in monkey is indicative of extensive first pass effect and in agreement with low bioavailability in monkey. In vitro metabolism in liver microsomes from the toxicological test species, mouse and dog, and humans was similar and there were no unique human metabolites. The N-demethylated metabolite M1 (KO-516) and metabolite M9 (KO-739) were identified as the major metabolites in mouse, dog, and human liver microsomal incubations. However, the human AME study demonstrated that both metabolites were minor, accounting for <10% of total drug-related exposure, thus not requiring further evaluation of the metabolites.
In Vivo
Pharmacokinetics, Distribution, Metabolism, and Excretion of 14C-KO-539 Following Oral Administration to Mice / Study KO-ADME-0044 / Section 5.2.2 of Module 2.6.4, Section 11 of Module 2.6.5

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Identification of KO-539 In Vitro and In Vivo Metabolites / Study KO-ADME-0049 / Section 5.2.1 of Module 2.6.4, Section 11 of Module 2.6.5

After single oral dosing of ziftomenib to MV4;11-tumor-bearing nude mice, KO-516 represented a major circulating metabolite in mouse with 35% area AUC_{last} exposure of ziftomenib in plasma. When in vivo metabolism of ziftomenib was evaluated in excreta from CD-1 mice after single IV administration of 50 mg/kg unlabeled ziftomenib, metabolites KO-516 and KO-739 were found to be greater than 10% of the sum of peak areas in plasma and feces.

Evaluation of the in vivo metabolism in plasma after single oral administration of [¹⁴C]ziftomenib to male and female BALB/c mice showed that the major circulating radioactive component was unchanged ziftomenib, accounting for 19.4% and 8.09% of the total radioactivity in AUC in male and female mice plasma, respectively. No single metabolite represented >10% of the total radioactivity. Of the 5 metabolites that were identified, KO-739 (M9) was the abundant circulating metabolite and accounted for 8.47% of total radioactivity exposure in male mice, and KO-739 (M9) was not identified in plasma from female mice. The KO-516/N-[des-N-methylsulfoxide-pyrazinyl]-oxy-KO-516 (M1/M6) mixture was an abundant component in males and females and accounted for 6.30% and 5.77% of total radioactivity exposure, respectively. These data are in agreement with the human AME data, which demonstrated that all metabolites were minor (<10% of total drug-related exposure).

In feces, unchanged ziftomenib accounted for 56.8% and 51.1% of the total dose in male and female mouse, respectively. Of the minor metabolites identified, KO-739 (M9) was the most abundant, accounting for 9.47% and 9.24% of the dose in males and females, respectively. KO-516 (M1) accounted for 4.83% and 5.77% in fecal samples from males and females, respectively. In urine, trace levels of ziftomenib and metabolites were excreted, representing 1.35% and 1.60% of administered radioactivity in males and females, respectively.

CYP Enzyme Reaction Phenotyping for ziftomenib using human hepatocytes, human recombinant CYP enzyme isoforms, and human liver microsomes / Studies KO-ADME-0048, KO-ADME-0050, and KO-ADME-0056 / Section 5.1.1.4 of Module 2.6.4, Section 10 of Module 2.6.5

All studies demonstrated that ziftomenib was metabolized by cytochrome P450 (CYP) 3A4, as the predominant isoform, and to a lesser extent by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2J2. PBPK modeling using clinical data demonstrated that there were no clinically relevant DDIs between ziftomenib and strong CYP3A4 inhibitors such as itraconazole. This is described in Section 8.

CYP Enzyme Inhibition by ziftomenib in Human Liver Microsomes / Studies KO-ADME-0065 and KO-ADME-0060 / Section 5.1.1.5 of Module 2.6.4, Section 13 of Module 2.6.5

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Komzifti (ziftomenib)

In the first study, direct inhibition by ziftomenib (0.05 to 50 μM) was observed for CYP3A4 (IC_{50} 12.2 μM ; midazolam as substrate), CYP2C19 (IC_{50} 11.2 μM), CYP2C9 (IC_{50} 9.48 μM), and CYP2C8 (IC_{50} 20.6 μM). Preincubation of ziftomenib with human liver microsomes for 30 minutes prior to addition of the NADPH-regenerating system shifted the IC_{50} value to 2.86 μM for CYP3A4 (midazolam) inhibition, suggesting a mild propensity for TDI of CYP3A4. In the second study, ziftomenib at lower concentrations (0.005 to 5 μM) directly inhibited CYP3A4/5 activity (midazolam 1'-hydroxylation) with an IC_{50} value of 1.9 μM . Ziftomenib was a metabolism-dependent inhibitor of CYP3A4/5; IC_{50} values shifted from 1.9 μM to 0.22 μM (midazolam) and >5 μM to 0.44 μM (testosterone). The R values suggest that a clinically relevant DDI is possible following co-administration of a CYP3A4 substrate. However, PBPK modeling using clinical data demonstrated that there were no DDIs between ziftomenib and CYP3A4 substrates such as midazolam..

UGT Inhibition by ziftomenib in Human Liver Microsomes / Study KO-ADME-0061 / Section 5.1.1.6 of Module 2.6.4, Section 13 of Module 2.6.5

Ziftomenib (0.0225 to 22.5 μM) was incubated (37°C) with microsomes, cofactor, and probe substrates specific for UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15, or UGT2B17. Samples were analyzed by LC-MS/MS. Ziftomenib directly inhibited UGT1A1, UGT1A9, and UGT2B17 with IC_{50} values of 3.4, 1.4, and 1.1 μM , respectively. At the clinical dose of 600 mg once daily, unbound ziftomenib mean C_{max} at steady state ($C_{\text{max,ss}}$) is expected to be approximately 0.1 μM , which is significantly lower than the IC_{50} of UGT inhibition. Thus, these in vitro data are not expected to be clinically relevant.

CYP Enzyme Induction by ziftomenib / Studies KO-ADME-0059, KO-ADME-0066 / Section 5.1.1.7 of Module 2.6.4, Section 13 of Module 2.6.5

Ziftomenib resulted in a 2.19- to 2.94-fold induction in CYP1A2 mRNA across the 3 donors tested, compared to >36 -fold inductions with the positive control (Study KO-ADME-0066). In a subsequent analysis using a broad concentration range, ziftomenib resulted in concentration-dependent increases in CYP1A2 mRNA up to 4.86-fold with maximal fold induction (E_{max}) values ranging from 1.87- to 2.86-fold change and 50% maximal effect (EC_{50}) values of induction ranging from 0.976 to 2.82 μM (Study KO-ADME-0059). In both studies, ziftomenib was considered an in vitro inducer of CYP1A2 but not CYP2B6 or CYP3A4. At the dose of 600 mg once daily, unbound ziftomenib mean $C_{\text{max,ss}}$ is expected to be approximately 0.1 μM , which is significantly lower than the EC_{50} of CYP1A2 induction. Thus, these in vitro data are not expected to be clinically relevant.

Excretion

Pharmacokinetics, Distribution, Metabolism, and Excretion of 14C-KO-539 Following Oral Administration to Mice / Study KO-ADME-0044 / Section 6.1 of Module 2.6.4, Section 14 of Module 2.6.5

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Urinary and Fecal Excretion of KO-539 and Its Major Metabolite M1 (KO-516) in Mice After an Intravenous Bolus Dose / KO-ADME-0063 / Section 6.2 of Module 2.6.4, Section 14 of Module 2.6.5

Based on a study with oral administration of [¹⁴C]ziftomenib in BALB/c mice, radioactivity was mainly excreted via the fecal route. At 168 h postdose, approximately 86.0% of the total dose was recovered in feces in males and females. Urinary excretion played a minor role, and approximately 1.5% of the dose was recovered in urine in males and females.

In excreta from CD-1 mice after single IV bolus administration of 25 and 50 mg/kg ziftomenib approximately 2.4% and 2.8% of unchanged ziftomenib was excreted through bile into feces during 48 h postdose, after 25 and 50 mg/kg dosing, respectively. Biliary excretion of KO-516 comprised approximately 2.4% of the administered ziftomenib dose at both dose levels tested. Approximately 0.04% and 0.25% of unchanged ziftomenib was excreted through urine during the first 48 h following a single IV administration at 25 and 50 mg/kg, respectively, whereas renally excreted KO-516 comprised approximately 0.01% of the administered ziftomenib dose at both dose levels.

Summary PK parameters from pharmacokinetic studies**Mean Plasma PK Parameters of Ziftomenib in Female Mice, Rats, Dogs, and Monkeys Following Single IV Administrations (KO-ADME-0032, KO-ADME-0033, Study KO-ADME-0034, KO-ADME-0035)**

Species	Actual Dose (mg/kg)	t _{1/2} (h)	CL (mL/min/kg)	V _{ss} (L/kg)	AUC _{last} (ng•h/mL)	AUC _{inf} (ng•h/mL)
Mouse/BALB/c	2.29	3.5	8.7	2.7	4325	4363
Rat/Sprague Dawley	1.78	10	20.3	14.2	1225	1451
Dog/beagle	1.80	11.6	17.0	13.2	1697	1786
Monkey/cynomolgus	1.90	9.1	20.7	7.3	1523	1544

Mean Plasma Pharmacokinetic Parameters of Ziftomenib in Female Mice, Rats, Dogs, and Monkeys Following Single Oral Administrations (KO-ADME-0032, KO-ADME-0033, Study KO-ADME-0034, KO-ADME-0035)

Species	Dose (mg/kg)	t _{max} (h)	C _{max} (ng/mL)	AUC _{last} (ng•h/mL)	AUC _{inf} (ng•h/mL)	Bioavailability (%)
Mouse/BALB/c	10	1.0	585	6273	6411	34
Rat/Sprague	10	4.7	122	1664	2067	24

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Dawley						
Dog/beagle	10	2.7	191	3285	4218	35
Monkey/cynomolgus	10	4.0	71.7	941	1992	11

Integrative summary table of C_{max} and AUC parameters across toxicology studies

CD-1 mice: TK parameters following 28-day oral repeat dose administration of ziftomenib (KO-TOX-0009)

Mean TK Parameters		40 mg/kg/day		120 mg/kg/day		400/200 mg/kg/day ^a	
		M	F	M	F	M	F
C _{max} (ng/mL)	Day 1	1470	1570	4000	3900	6500	7050
	Day 29	1690	2070	3560	4000	4890	5290
AUC ₀₋₂₄ (ng•h/mL)	Day 1	17,000	20,800	55,900	54,200	118,000	126,000
	Day 29	19,900	22,900	62,800	64,600	93,500	97,300
Accumulation Ratio (AUC ₀₋₂₄) Day 29/Day1		1.17	1.10	1.12	1.19	NA ^c	NA ^c

CD-1 mice : Mean TK parameters following 13-week oral repeat dose administration of ziftomenib (KO-TOX-0010)

Mean TK Parameters		12 mg/kg/day		40 mg/kg/day		120 mg/kg/day	
		M	F	M	F	M	F
C _{max} (ng/mL)	Day 1	346	422	1610	1960	3960	4280
	Day 91	270	367	1380	1900	3280	2810
AUC ₀₋₂₄ (ng•h/mL)	Day 1	3610	4200	18,300	20,200	50,600	61,500
	Day 91	3510	3940	17,200	24,000	57,300	53,100
Accumulation Ratio (AUC _{0-t}) Day 91/Day1		0.973	0.937	0.940	1.19	1.13	0.862

^a Due to evidence of excessive toxicity, surviving TK animals at 400 mg/kg/day were placed on a 3-day dosing holiday beginning on Day 9, and resumed dosing on Day 12 at a reduced dose level of 200 mg/kg/day for the remainder of the study.

^b T_{max} collection intervals were determined from the first daily dose: T_{max} values greater than 6 h occurred following the second daily dose.

^c Accumulation ratios could not be determined due to the reduction in dose level for TK animals at 400/200 mg/kg/day beginning on Day 12
data represent mean of n=3 animals / sex/ timepoint

Beagle dogs: TK parameters following 28-day oral repeat dose administration of ziftomenib (KO-TOX-0012)

Mean TK Parameters		20 mg/kg/day		60 mg/kg/day		200 mg/kg/day	
		M	F	M	F	M	F

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C _{max} (ng/mL)	Day 1	213	226	1190	1180	3030	3090
	Day 28	358	327	1040	1250	1810	2130
AUC ₀₋₂₄ (ng•h/mL)	Day 1	3360	2940	15,900	16,900	43,800	42,800
	Day 28	5810	4800	19,700	25,200	32,900	43,900
Accumulation Ratio (AUC ₀₋₂₄) Day 28/ Day 1		1.77	1.64	1.26	1.51	0.744	1.08
Beagle dogs: TK parameters following 13-week oral repeat dose administration of ziftomenib (KO-TOX-0012)							
Mean TK Parameters		6 mg/kg/day		20 mg/kg/day		60 mg/kg/day	
		M	F	M	F	M	F
C _{max} (ng/mL)	Day 1	57.3	59.5	294	294	1420	1110
	Day 91	33.7	49.1	274	271	726	780
AUC _{last} (ng•h/mL)	Day 1	695	714	3960	3660	18,700	15,800
	Day 91	699	853	5100	4930	15,300	15,300
Accumulation Ratio (AUC _{last}) Day 91// Day 1		1.02	1.23	1.29	1.34	0.856	1.06
data represent mean of n=4 animals / sex							
Pregnant Mice: TK parameters oral repeat dose administration of ziftomenib from GD6 through GD15 (KO-TOX-0018)							
Mean TK parameters in Dams		6 mg/kg/day		20 mg/kg/day		60 mg/kg/day	
C _{max} (ng/mL) - GD 6		260		979		2640	
C _{max} (ng/mL) - GD 15		237		996		2190	
AUC ₀₋₂₄ (ng•h/mL) - GD 6		2610		12,000		35,000	
AUC ₀₋₂₄ (ng•h/mL) - GD 15		3430		14,500		34,900	

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment. See Sections 6 and 14 for FDA's assessment of drug-drug interaction (DDI) studies.

Toxicokinetics

In the 7-day repeat-dose toxicology studies in mice and dogs, exposure (C_{max} and AUC) increased with increasing dose, but in a manner that was less than dose-proportional. In the 28-day repeat-dose toxicology studies in mice and dogs, exposure increased with increasing dose in a manner that was dose-proportional or less than dose-proportional. In the 13-week repeat-dose toxicology studies in mice and dogs, exposure increased in a manner that was dose-proportional in mice but greater than dose-proportional in dogs with increasing dose. Exposure was similar in males and females for the 7-day, 28-day, and 13-week studies.

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5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Ziftomenib is a menin inhibitor intended for the treatment of advance hematologic malignancies. The ziftomenib toxicology program was designed in accordance with ICH S9 guidance and other relevant ICH guidances on safety. All pivotal studies were conducted in accordance with GLP and currently accepted guidelines. Ziftomenib was tested in a single-dose study in mice and exploratory 7-day dose-range finding studies in mice and dogs. The definitive nonclinical safety program was comprised of 28-day and 13-week toxicity studies in mice and dogs, as well as the standard battery of genetic toxicology studies, in vitro and in vivo phototoxicity studies, and an embryofetal development study in mice.

Pivotal Repeat Dose Toxicity Studies

28-Day Oral Gavage Toxicity and Toxicokinetic Study of KO-539 in Mice with a 28-Day Recovery Period / Study No. KO-TOX-0009 / Section 3.2 of Module 2.6.6, Section 7.1.1 of Module 2.6.7

Key Drug-related Adverse Findings

- Dose limiting toxicities (adverse body weight loss and dehydration) were observed at 400 mg/kg/day the high dose was adjusted to 200 mg/kg/day (Day 12/14). Unscheduled deaths (Day 17 and Day 22) were due to body weight loss and dehydration and likely contribution of histopathologically, ziftomenib-related microscopic findings in the liver, kidney, lung, spleen, and lymph nodes.
- In scheduled sacrificed animals adverse microscopic findings at the terminal necropsy were noted in the liver, lung, kidney, spleen, and lymph nodes (mandibular, axillary, and mesenteric).

GLP compliance: Yes

Methods

Dose and frequency of dosing:

0 mg/kg bid (0 mg/kg/day), 20 mg/kg bid (40 mg/kg/day), 60 mg/kg bid (120 mg/kg/day), and 200/100 mg/kg bid (400/200 mg/kg/day) for 28 days. Daily doses were administered at least 6 hours, but not more than 7 hours, apart.

Dose-limiting toxicity was observed at; 400 mg/kg/day after approximately 1 week of dosing. Adverse body weight loss (in some instances, greater than -15% on Day 8 vs Day 1) and dehydration were noted. Beginning on Day 9/11 high-dose

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	animals were allowed a 3-day dosing holiday; dosing resumed beginning on Day 12/14 at a reduced dose level of 200 mg/kg/day.
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) ® in reverse osmosis deionized water with 3.0 molar equivalent (b) (4) pH (b) (4)
Species/Strain:	Mouse/CD-1
Number/Sex/Group:	20/sex/group (recovery: vehicle, n=10/sex; high dose 6M, 10F)
Age:	Approximately 11 weeks of age at initiation of dosing
Satellite groups:	Toxicokinetics satellite group 6 (vehicle) 54 (treatment) animals/sex

Observations and Results:	
Parameters	Major findings
Mortality	Three unscheduled deaths in males from the high-dose group were considered related to ziftomenib administration. These males were euthanized in extremis (2 on Day 17 and 1 on Day 22) due to adverse body weight loss and worsening clinical condition. Clinical observations generally noted for these animals prior to termination included suspected dehydration, unkempt appearance, hunched posture, decreased feces, pale skin (generalized), decreased activity, and/or cold to touch. On the day of euthanasia, body weight values for these males was decreased (-27% to -33%) versus respective Day 1 values. Although a definitive cause of moribundity could not be determined histopathologically, ziftomenib-related microscopic findings in the liver, kidney, lung, spleen, and lymph nodes were considered contributory.
Clinical signs	At scheduled termination, ziftomenib-related clinical observations were limited to generally low frequencies of delayed skin turgor and eyes partly closed among high-dose males and/or females. Additionally, limited occurrences of dehydration were noted for high-dose males during veterinary examination.
Body weight	Beginning on Day 15 and continuing through the end of the recovery period, mean body weight values for high-dose males and females were generally comparable to, and occasionally greater than, the respective concurrent control values.
Food consumption	No noteworthy findings

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Observations and Results:									
Ophthalmology	No noteworthy findings								
Hematology	Dose-dependent decreased erythrocyte mass (mean red blood cell counts, hemoglobin, and hematocrit values) were observed in both sexes at all dose levels evaluated. Additionally, RBC distribution width was mildly increased in both sexes.								
	Parameter	Male				Female			
	Dose (mg/kg/day)	0	40	120	400/200	0	40	120	400/200
	Number of animals	20	20	20	20	20	20	20	20
	Red Blood Cell Count (10 ⁶ /μL)	10.50	9.64*	9.19*	8.74**	10.46	9.55*	9.22*	8.95**
	Hemoglobin (g/dL)	15.8	14.9*	14.3*	13.3**	15.7	14.9	14.3*	13.7**
	Hematocrit (%)	52.4				52.4			
	Red Blood Cell Distribution Width (%)	12.1	12.2	12.8*	13.6**	12.2	13.0	12.7	13.8
Clinical chemistry	Key findings include increased mean ALT, AST and sorbitol dehydrogenase (SDH) activities in both sexes at the mid- and high-dose levels.								
	Parameter	Male				Female			
	Dose (mg/kg/day)	0	40	120	400/200	0	40	120	400/200
	Number of animals	20	20	20	20	20	20	20	20
	ALT (U/L)	184	259	304	576**	147	126	219	385**
	AST (U/L)	175	205	186	383**	163	138	199	308**
	SDH (U/L)	84	130	180	355**	51	47	92	231**
Gross pathology	At the mid and high dose level ziftomenib-related macroscopic findings included green liver discoloration in both sexes and axillary and/or inguinal								

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Komzifti (ziftomenib)

Observations and Results:							
	lymph node enlargement due to sinus histiocytosis noted in a single female each at the mid- and high-dose levels.						
Organ weights	Ziftomenib-related increases (vs concurrent control values) in mean liver, kidney, spleen, adrenal gland, and heart weight parameters (absolute and/or relative to body and/or brain weight) were noted for both sexes at the terminal necropsy.						
	Organ Tissue	Male			Female		
	Dose (mg/kg/day)	40	120	400/200	40	120	400/200
	Number of animals	20	20	20	20	20	20
	Adrenal Gland						
	% absolute			+41.24*			+27.95*
	% relative BW	-4.45	+20.92*	+32.47*	+2.33	+18.93*	*
	% relative Brain Weight	-6.41	+12.89	*	-3.11	+6.63	+16.55*
		-3.18	+19.74*	+38.27*	+1.22	+19.74*	+26.56*
				*			*
Heart							
% absolute		+13.37*			+16.12*	+14.36*	
% relative BW	+6.35	*	+10.59*	+7.61	*	*	
% relative Brain Weight	+3.81	+5.43	+3.18	+1.89	+4.66	+4.51	
	+8.23	+12.33*	+8.70	+6.39	+16.80*	+13.15*	
		*			*	*	
Kidney							
% absolute		+19.66*	+21.01*		+14.77*	+19.60*	
% relative BW	+11.92*	*	*	+5.00	*	*	
% relative Brain Weight	+9.40*	+11.18*	+12.57*	-0.2	+3.46	+9.35*	
	+13.75*	*	*	+3.75	+15.29*	+18.41*	
	*	+18.36*	+18.61*		*	*	
		*	*				
Liver							
% absolute	+4.66	+22.95*	+58.32*	+10.0	+30.59*	+61.47*	
	+2.18	*	*	0	*	*	

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Komzifti (ziftomenib)

Observations and Results:									
	% relative BW	+6.35	+13.82*	+47.90*	+4.39	+17.91*	+47.57*		
			*	*	+8.78	*	*		
	% relative Brain Weight		+21.72*	+55.44*		+31.34*	+59.58*		
			*	*		*	*		
	Spleen								
	% absolute			+37.55*	+12.6		+32.16*		
	% relative BW	-6.17	+2.24	*	0	+12.48	*		
% relative Brain Weight	-8.39	-4.99	+28.32*	+6.64	+1.51	+20.43*			
	-4.79	+0.8	*	+11.1	+13.20	*			
			+34.52*	0		*			
Percent differences from controls are shown. Statistical significance is based on actual data (not on the percent difference values). Due to evidence of excessive toxicity, beginning on Day 9/11 (F/M), all high-dose (200 mg/kg/dose bid; 400 mg/kg/day) animals were allowed a 3-day dosing holiday. Animals resumed dosing on Day 12/14 (F/M) at a reduced dose level of 100 mg/kg/dose bid; 200 mg/kg/day.									
Histopathology	Ziftomenib-related microscopic findings at the terminal necropsy were noted in the liver, lung, kidney, spleen, and lymph nodes (mandibular, axillary, and mesenteric).								
	Organ Tissue	Male				Female			
	Dose mg/kg bid	0	20	60	200/100	0	20	60	200/100
	mg/kg/day	0	40	120	400/200	0	40	120	400/200
	Number examined	10	10	10	10	10	10	10	10
	Kidney								
	Rarefaction, Cytoplasmic; Tubular, Inner Stripe of the Outer Medulla	0	0	5	10	0	0	3	10
	Minimal	0	0	4	3	0	0	0	4
	Mild	0	0	1	4	0	0	3	4
	Moderate	0	0	0	3	0	0	0	2
Liver									
Cytoplasmic Alteration/Pigment;	0	4	10	10	0	1	10	10	

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Komzifti (ziftomenib)

Observations and Results:									
	Hepatocellular, Kupffer Cell								
	Minimal	0	4	3	0	0	1	8	0
	Mild	0	0	6	5	0	0	2	9
	Moderate	0	0	1	5	0	0	0	1
	Infiltration, Histiocytic	0	0	8	10	0	0	1	10
	Minimal	0	0	8	1	0	0	1	4
	Mild	0	0	0	6	0	0	0	5
	Moderate	0	0	0	3	0	0	0	1
	Hypertrophy, Centrilobular, Hepatocellular	0	0	5	8	0	0	3	1
	Minimal	0	0	2	4	0	0	3	1
	Mild	0	0	3	4	0	0	0	0
	Regeneration; Hepatocellular, Multifocal	0	1	5	6	0	1	2	4
	Minimal	0	1	5	6	0	1	2	1
	Mild	0	0	0	0	0	0	0	3
	Degeneration/Necrosis ; Hepatocellular, Multifocal	0	0	0	8	0	0	1	8
	Minimal	0	0	0	8	0	0	1	8
	Lung								
	Vacuolation Accumulation, Cytoplasmic, Histiocytic Cell	0	5	9	10	0	1	8	10
	Minimal	0	5	2	0	0	1	4	0
	Mild	0	0	7	10	0	0	4	10
	Increased Cellularity; Alveolar, Histiocytic Cell	0	0	7	10	0	2	4	10
	Minimal	0	0	5	4	0	2	3	2
	Mild	0	0	2	5	0	0	1	6
	Moderate	0	0	0	1	0	0	0	2

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Komzifti (ziftomenib)

Observations and Results:									
	Lymph Node, Mesenteric								
	Vacuolation Accumulation, Cytoplasmic, Histiocytic Cell	0	0	10	10	0	1	9	10
	Minimal	0	0	3	4	0	1	3	3
	Mild	0	0	7	4	0	0	5	5
	Moderate	0	0	0	2	0	0	1	2
	Sinus Histiocytosis	4	0	4	9	2	0	6	9
	Mild	4	0	4	5	2	0	4	3
	Moderate	0	0	0	3	0	0	2	6
	Marked	0	0	0	1	0	0	0	0
	Lymph Node, Axillary								
	Vacuolation Accumulation, Cytoplasmic, Histiocytic Cell	0	0	7	8	0	0	6	9
	Minimal	0	0	5	4	0	0	5	6
	Mild	0	0	2	4	0	0	1	3
	Sinus Histiocytosis	0	0	2	3	1	0	2	6
	Mild	0	0	0	0	0	0	0	1
	Moderate	0	0	2	2	1	0	2	4
	Marked	0	0	0	1	0	0	0	1
	Lymph Node, Mandibular								
	Vacuolation Accumulation, Cytoplasmic, Histiocytic Cell	0	0	5	9	0	0	4	9
	Minimal	0	0	4	4	0	0	4	3
	Mild	0	0	1	4	0	0	0	5
	Moderate	0	0	0	1	0	0	0	1
	Spleen								
	Increased Cellularity; Histiocytic	0	0	2	10	0	0	2	10

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Komzifti (ziftomenib)

Observations and Results:									
	Cell/Eosinophilic Granular Cytoplasm								
	Minimal	0	0	2	3	0	0	2	0
	Mild	0	0	0	4	0	0	0	7
	Moderate	0	0	0	2	0	0	0	3
	Marked	0	0	0	1	0	0	0	0
Other relevant evaluations	As evidence of bilirubin staining (characterized by the presence of green material using light microscopy) was not observed for any animal at either necropsy interval, the granular eosinophilic/golden material within centrilobular hepatocytes was not interpreted to be bile and/or bile-containing material. Transmission electron microscopy (TEM) revealed an increased number of and/or larger lysosomes containing phospholipid material (in lamellar, concentric, and/or myelinoid aggregates, with rare multivesiculate bodies) within the cytoplasm of pulmonary alveolar macrophages of high-dose terminal necropsy animals when compared with lysosomes of vehicle-treated concurrent control animals. The increased incidence and/or severity of accumulation of lysosomal phospholipid material in alveolar macrophages was consistent with a diagnosis of phospholipidosis. Also within the high-dose recovery animals evaluated, increased numbers of and/or larger lysosomes containing phospholipid material were observed within the cytoplasm of pulmonary alveolar macrophages, consistent with phospholipidosis. However, these lysosomes were less prominent and numerous than those observed in high-dose animals at the terminal necropsy, suggesting a lack of nascently retained phospholipid material. Additionally, the presence of more numerous telolysosomes (lysosomes having accumulated indigestible/end-stage material such as lipofuscin) in high-dose recovery animals was considered to represent the progression of lysosomal digestion								
Toxicokinetics	Systemic exposure to ziftomenib and KO-516 (metabolite) was independent of sex. C_{max} values for ziftomenib and KO-516 increased with increasing dose in a less-than-dose-proportional manner on Days 1 and 29. AUC_{0-24h} values for ziftomenib and KO-516 increased with increasing dose in an approximately dose-proportional manner from 40 to 120 mg/kg/day and in a less-than-dose-proportional manner from 40 to 400 mg/kg/day on Day 1. On Day 29, AUC_{0-24h} values for ziftomenib and KO-516 increased with increasing dose in an approximately dose-proportional manner from 40 to 200 mg/kg/day. Systemic exposure to ziftomenib and KO-516 did not change following repeated bid administration of ziftomenib. Systemic exposure (AUC_{0-24h}) to KO-516 was approximately 23% to 33% of the systemic exposure of ziftomenib.								

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Komzifti (ziftomenib)

Observations and Results:						
	Toxicokinetics Overview					
	Ziftomenib (mg/kg/day)	Day	Ziftomenib^a		KO-516^a	
			Cmax (ng/mL)	AUC0-24h (ng*hr/mL)	Cmax (ng/mL)	AUC0-24h (ng*hr/mL)
	40	1	1520	18,900	463	6210
		29	1850	21,400	500	6290
	120	1	3950	55,000	1130	15,900
		29	3540	63,700	994	18,500
400/200 ^b	1	6780	122,000	1430	28,300	
	29	5090	95,400	1360	26,400	
Abbreviations: AUC=area under the plasma concentration-time curve; AUC0-24h=area under the plasma concentration-time curve from time 0 to 24 hours; bid=twice daily; Cmax=maximum plasma concentration. a Systemic exposure to ziftomenib and KO-516 was independent of sex; therefore, data are reported as combined-sex values (mean). b Due to evidence of excessive toxicity, beginning on Day 9, all Group 4 TK animals were allowed a 3-day dose holiday; dosing resumed on Day 12 at a reduced dose level of 100 mg/kg/dose bid (200 mg/kg/day). Under the conditions of this study, the STD10 of ziftomenib was considered to be greater than 120 mg/kg/day but less than 400/200 mg/kg/day. Combined-sex systemic exposure (Cmax and AUC0-24h) to ziftomenib at 120 mg/kg/day on Day 29 was 3540 ng/mL and 63,700 ng*hr/mL, respectively. Corresponding values for the KO-516 metabolite were 994 ng/mL and 18,500 ng*hr/mL, respectively.						
Observations and Results: Recovery Groups						
Hematology	Changes of RDW fully recovered, decreases in erythrocyte mass, persisted in high-dose animals at the end of the recovery period, however, were of a lesser magnitude relative to the terminal collection, suggestive of partial recovery					
Clinical chemistry	Increases in liver enzyme activity persisted in high-dose animals at the end of the recovery period, they were of lesser magnitude relative to the terminal collection, suggestive of partial recovery.					
Gross pathology	All resolved.					
Organ weights	Mean liver and kidney weight parameters remained increased (vs concurrent control values) in high-dose animals, although with evidence of partial recovery. Spleen, adrenal gland, and heart weight parameters remained					

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Komzifti (ziftomenib)

Observations and Results:	
	increased in both sexes, with microscopic correlates similar to those noted at the terminal necropsy.
Histopathology	At the recovery necropsy, ziftomenib-related microscopic findings in high-dose animals persisted with partial recovery in the lung, liver, kidney, spleen, and lymph nodes (mandibular, axillary, and mesenteric).

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NDA 220305

Komzifti (ziftomenib)

A 13-Week (Twice Daily) Oral Gavage Toxicity and Toxicokinetic Study of KO-539 in Mice with a 28-Day Recovery Period/ Study No. KO-TOX-0010/ Section 3.3 of Module 2.6.6, Section 7.1.2 of Module 2.6.7

Key Drug-related Adverse Findings

- Key Adverse findings were cytoplasmic alteration/pigment and hepatocellular hypertrophy present in the liver of both sexes at 120 mg/kg/day at the terminal necropsy which were associated with increases in serum AST and ALT activities and total bilirubin concentration.

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 mg/kg bid (0 mg/kg/day), 6 mg/kg bid (12 mg/kg/day), 20 mg/kg bid (40 mg/kg/day), and 60 mg/kg bid (120 mg/kg/day). Daily doses were administered at least 6 hours, but not more than 7 hours, apart.
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) in reverse osmosis deionized water with 3.0 molar equivalent (b) (4) pH (b) (4) solution.
Species/Strain:	Mouse/CD-1
Number/Sex/Group:	20 animals/sex/group (recovery: vehicle and high dose group 10 animals/group)
Age:	Approximately 9 weeks
Satellite groups:	Toxicokinetics satellite group 6 (vehicle) 54 (treatment) animals/sex

Observations and Results: Main Study Groups	
Parameters	Major findings
Mortality	9 animals (4 Main Study and 5 TK Study) in the control, 12, 40, and 120 mg/kg/day groups were found dead or euthanized in moribund condition during the treatment period. All deaths were considered unrelated to ziftomenib administration. All other animals survived until scheduled termination.
Clinical signs	No noteworthy findings
Body weight	Ziftomenib-related increased (vs control) mean body weight was noted throughout the study for both sexes at 40 mg/kg/day (F: 9%) and 120 mg/kg/day (M: 9%; F: 19%).

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Komzifti (ziftomenib)

Food consumption	No noteworthy findings								
Ophthalmology	No noteworthy findings								
Hematology	Dose-dependent decreases in mean RBC counts, hemoglobin, and hematocrit in males and females at ≥ 40 mg/kg/day and a mildly decreased RETIC in males at ≥ 40 mg/kg/day were observed at the end of the dosing period (Day 92).								
	Parameter	Male				Female			
	Dose mg/kg/day	0	12	40	120	0	12	40	120
	No animals	20	20	20	20	20	20	20	20
	Red Blood Cells ($10^6/\mu\text{L}$)	9.88	9.47	8.82*	8.48*	9.87	9.50	8.89*	8.44*
	Hemoglobin (g/dL)	14.59	14.34	13.18**	12.12**	15.16	14.66	13.89**	13.00**
	Hematocrit (%)	50.34	49.71	45.18**	42.91**	51.95	50.01	47.57**	44.47**
	Reticulocyte ($10^9/\text{L}$)	315.56	291.78	249.06*	259.97	293.86	250.04	258.80	295.77
* $p \leq 0.05$ and ** $p \leq 0.01$ when compared to the control group using Dunnett's/Dunn's test.									
Clinical chemistry	Findings at the end of the dosing period included increased mean serum AST activity in males at 120 mg/kg/day and in females at ≥ 40 mg/kg/day, dose-dependent increased mean serum ALT activity in both sexes at ≥ 40 mg/kg/day, minimally increased mean serum total bilirubin concentration in both sexes at 120 mg/kg/day, and minimally increased mean serum calcium concentration in females at 120 mg/kg/day.								
	Parameter	Male				Female			

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Komzifti (ziftomenib)

	Dose mg/kg/ bid mg/kg/d ay	0 0	6 12	20 40	60 120	0 0	6 12	20 40	60 120
	No of animals	20	20	20	20	20	20	20	20
	AST (U/L)	94. 0	139. 7	121. 0	174.2* *	124. 0	133. 9	210.1 *	256.8* *
	ALT (U/L)	93. 3	146. 8	148. 5	280.4* *	134. 7	147. 1	206.7	367.3* *
	Total bilirubin (mg/dL)	0.0 9	0.10	0.12	0.15**	0.05	0.06	0.06	0.12**
	Calcium (mg/dL)	9.2 2	9.10	9.18	9.52*	9.01	9.00	9.07	9.48**
Gross pathology	Findings on Day 92 included dark red discoloration of the liver, which was noted macroscopically for both sexes at 120 mg/kg/day at the terminal necropsy (M:16/20; F: 12/20)								
Organ weights	At the terminal necropsy, increased (vs control) mean organ weight parameters for the adrenal gland, heart, kidney, liver/gallbladder, pituitary, spleen, thyroid/parathyroid, and thymus were noted.								
Histopathology	Microscopically, nonadverse subcapsular hyperplasia of the adrenal gland was observed at 120 mg/kg/day. Adverse findings of cytoplasmic alteration/pigment and hepatocellular hypertrophy were present in the liver of both sexes at 120 mg/kg/day at the terminal necropsy								
	Organ / Tissue	Male				Female			
	Dose mg/kg bid	0	6	20	60	0	6	20	60
	mg/kg/day	0	12	40	120	0	12	40	120
	Number examined	10	10	10 ^a	10	10	10	8	10
	Liver								
	Cytoplasmic Alteration/Pigment; Eosinophilic	0	0	0	10	0	0	0	10
	Minimal	-	-	-	4	-	-	-	1
	Mild	-	-	-	2	-	-	-	6
	Moderate	-	-	-	4	-	-	-	3
Hypertrophy; Hepatocellular	0	3	8	9	0	0	0	9	
Minimal	-	3	2	2	-	-	-	7	
Mild	-	0	5	4	-	-	-	2	

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Komzifti (ziftomenib)

	Moderate	-	0	1	3	-	-	-	0	
	^a adrenal gland n=9									
other relevant evaluations	None									
Toxicokinetics	Systemic exposure (C_{max} and AUC_{0-24h}) to ziftomenib and its 2 metabolites, KO-516 and KO-739, increased with increasing dose in a generally dose-proportional or greater-than-dose-proportional manner across the dose range on both Days 1 and 91. There were no sex-related differences in exposure to any analyte and no accumulation of ziftomenib or its metabolites in plasma on Day 91 compared to Day 1. Exposure (AUC_{0-24h}) to ziftomenib was 3- to 4-fold greater than exposure to KO-516 and 3- to 6-fold greater than exposure to KO-739.									
	Ziftomenib (mg/kg/day)	Day	Ziftomenib							
			C _{max} (ng/mL)			AUC _{0-24h} (ng*hr/mL)				
			Males	Females	Males	Females	Males	Females		
	12	1	346	422	3610	4200				
		91	270	367	3510	3940				
	40	1	1610	1960	18,300	20,200				
		91	1380	1900	17,200	24,000				
	120	1	3960	4280	50,600	61,500				
		91	3280	2810	57,300	53,100				
	Ziftomenib (mg/kg/day)	Day	KO-516				KO-739			
			C _{max} (ng/mL)		AUC _{0-24h} (ng*hr/mL)		C _{max} (ng/mL)		AUC _{0-24h} (ng*hr/mL)	
			Males	Females	Males	Females	Males	Females	Males	Females
12	1	90.9	118	987	1210	126	80.2	1240	858	
	91	52.9	78.9	824	1000	54.0	50.5	768	671	
40	1	383	563	5020	6300	463	386	5380	4120	
	91	327	483	5010	7040	275	277	3960	4170	
120	1	927	1310	13,900	19,000	865	840	13,800	12,700	
	91	797	749	15,500	14,300	701	595	13,900	10,000	
Abbreviations: AUC=area under the plasma concentration-time curve; AUC _{0-24h} =area under the plasma concentration-time curve from time 0 to 24 hours; C _{max} =maximum plasma concentration										
Systemic exposure (C_{max} and AUC_{0-24h}) to ziftomenib at the NOAEL on Day 91 was 1380 ng/mL and 17,200 ng*hr/mL, respectively, in males and 1900 ng/mL										

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Komzifti (ziftomenib)

	and 24,000 ng*hr/mL, respectively, in females. Corresponding values for the KO-516 metabolite were 327 ng/mL and 5010 ng*hr/mL, respectively, in males and 483 ng/mL and 7040 ng*hr/mL, respectively, in females. Corresponding values for the KO-739 metabolite were 275 ng/mL and 3960 ng*hr/mL, respectively, in males and 277 ng/mL and 4170 ng*hr/mL, respectively, in females.																																																																																																			
Observations and Results: Recovery Groups Day 120																																																																																																				
Body weight	No noteworthy finding																																																																																																			
Hematology	The decreases in RBC counts, hemoglobin, and hematocrit persisted in males at 120 mg/kg/day and was partially reversed in females at 120 mg/kg/day, with a new finding of minimally decreased mean corpuscular hemoglobin (MCH) noted males at 120 mg/kg/day. Although the decrease in RBC mass persisted in males at 120 mg/kg/day, the decrease in reticulocytes had completed reversed.																																																																																																			
Clinical chemistry	There was partial reversibility in ALT activity in both sexes at 120 mg/kg/day, with complete reversibility in AST activity and total bilirubin and calcium concentrations in males and/or females																																																																																																			
Gross pathology	Red discoloration of the liver, which was noted macroscopically for both sexes at 120 mg/kg/day at the terminal necropsy was still present at the recovery necropsy in n=4 females																																																																																																			
Organ weights	At the recovery necropsy, mean organ weight values remained increased (vs control) for all affected organs with the exception of the thyroid/parathyroid.																																																																																																			
Histopathology	Findings of hepatocellular hypertrophy with cytoplasmic alteration/pigment of the liver were still present in both sexes,																																																																																																			
	<table border="1"> <thead> <tr> <th>Organ / Tissue</th> <th colspan="4">Male</th> <th colspan="4">Female</th> </tr> </thead> <tbody> <tr> <td>Dose mg/kg bid</td> <td>0</td> <td>6</td> <td>20</td> <td>60</td> <td>0</td> <td>6</td> <td>20</td> <td>60</td> </tr> <tr> <td>mg/kg/day</td> <td>0</td> <td>12</td> <td>40</td> <td>120</td> <td>0</td> <td>12</td> <td>40</td> <td>120</td> </tr> <tr> <td>Number examined</td> <td>9</td> <td>NA</td> <td>NA</td> <td>10</td> <td>10</td> <td>NA</td> <td>NA</td> <td>10</td> </tr> <tr> <td>Liver</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Cytoplasmic Alteration/Pigment; Eosinophilic</td> <td>0</td> <td>NA</td> <td>NA</td> <td>10</td> <td>0</td> <td>NA</td> <td>NA</td> <td>10</td> </tr> <tr> <td>Minimal</td> <td>-</td> <td>NA</td> <td>NA</td> <td>0</td> <td>-</td> <td>NA</td> <td>NA</td> <td>1</td> </tr> <tr> <td>Mild</td> <td>-</td> <td>NA</td> <td>NA</td> <td>7</td> <td>-</td> <td>NA</td> <td>NA</td> <td>7</td> </tr> <tr> <td>Moderate</td> <td>-</td> <td>NA</td> <td>NA</td> <td>3</td> <td>-</td> <td>NA</td> <td>NA</td> <td>2</td> </tr> <tr> <td>Hypertrophy; Hepatocellular</td> <td>1</td> <td>NA</td> <td>NA</td> <td>4</td> <td>0</td> <td>NA</td> <td>NA</td> <td>2</td> </tr> <tr> <td>Minimal</td> <td>1</td> <td>NA</td> <td>NA</td> <td>4</td> <td>-</td> <td>NA</td> <td>NA</td> <td>2</td> </tr> </tbody> </table>	Organ / Tissue	Male				Female				Dose mg/kg bid	0	6	20	60	0	6	20	60	mg/kg/day	0	12	40	120	0	12	40	120	Number examined	9	NA	NA	10	10	NA	NA	10	Liver									Cytoplasmic Alteration/Pigment; Eosinophilic	0	NA	NA	10	0	NA	NA	10	Minimal	-	NA	NA	0	-	NA	NA	1	Mild	-	NA	NA	7	-	NA	NA	7	Moderate	-	NA	NA	3	-	NA	NA	2	Hypertrophy; Hepatocellular	1	NA	NA	4	0	NA	NA	2	Minimal	1	NA	NA	4	-	NA	NA	2
	Organ / Tissue	Male				Female																																																																																														
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	Number examined	9	NA	NA	10	10	NA	NA	10																																																																																											
	Liver																																																																																																			
	Cytoplasmic Alteration/Pigment; Eosinophilic	0	NA	NA	10	0	NA	NA	10																																																																																											
	Minimal	-	NA	NA	0	-	NA	NA	1																																																																																											
	Mild	-	NA	NA	7	-	NA	NA	7																																																																																											
Moderate	-	NA	NA	3	-	NA	NA	2																																																																																												
Hypertrophy; Hepatocellular	1	NA	NA	4	0	NA	NA	2																																																																																												
Minimal	1	NA	NA	4	-	NA	NA	2																																																																																												
^a adrenal gland n=9																																																																																																				

NDA Multidisciplinary Review and Evaluation

NDA 220305

Komzifti (ziftomenib)

A 28-Day Oral Gavage Toxicity and Toxicokinetic Study of KO-539 in Beagle Dogs with a 28-Day Recovery Period/ Study No. KO-TOX-0012 / Section 3.5 of Module 2.6.6, Section 7.2.1 of Module 2.6.7

Key Drug-related Adverse Findings

- Microscopic findings that were considered adverse (at 200 mg/kg/day) included basophilic accumulations and increased cellularity of basophilic macrophages involving the liver, bile duct, gallbladder, and intestines; increased cellularity of vacuolated macrophages within the lymphoid organs, lymphoid depletion of the thymus, Peyer's patches, and lymph nodes, and membranous glomerulopathy. Findings persisted at the end of the recovery period.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 mg/kg bid (0 mg/kg/day), 10 mg/kg bid (20 mg/kg/day), 30 mg/kg bid (60 mg/kg/day), and 100 mg/kg bid (200 mg/kg/day). Daily doses were administered at least 6 hours, but not more than 7 hours, apart.
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) ® in reverse osmosis deionized water with 3.0 molar equivalent (b) (4) pH (b) (4)
Species/Strain:	Dog, Beagle
Number/Sex/Group:	4 animals/sex (vehicle and high dose group 2 animals/group)
Age:	Approximately 6 months of age at initiation of dosing
Satellite groups:	none

Observations and Results: Main Study Groups

Parameters	Major findings
Mortality	200 mg/kg/day: There were two unscheduled deaths of male animals during the dosing phase (Day 12 and Day 23) which were considered related to ziftomenib administration. The cause of mortality/moribundity was considered a secondary complication of ziftomenib-related clinical signs (primarily, emesis- and/or excreta- related findings) rather than a primary effect of the test article. Ziftomenib-related histopathological findings in primarily the hepatobiliary organs, gastrointestinal tract, lymphoid organs, and kidney also contributed to the demise of these two high-dose males.
Clinical signs	Ziftomenib-related clinical signs were mostly dose responsive and were

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Observations and Results: Main Study Groups																																																																
	generally observed with the greatest frequency at the high-dose level. They included included excreta-related findings (soft, liquid or mucoid feces and feces with particles) and suspected dehydration (high-dose females). Limited occurrences of vomitus were observed in both sexes at the mid- and high-dose levels. Thin body condition was noted for three high-dose females beginning on Day 18 and continuing through Day 29; single occurrences of thin body condition were observed on the day of terminal necropsy for a single male each at the mid- and high-dose levels.																																																															
Body weight	<i>200 mg/kg/day</i>: On Day 28, mean body weight values were 25.82% (males) and 27.66% (females) lower than concurrent control values. <i>60 mg/kg/day</i>: On Day 28, mean body weight values were 11.26% (males) and 14.18% (females) lower than concurrent control values.																																																															
Food consumption	<i>200 mg/kg/day</i>: In week 4 food consumption was statistically significantly decreased in high dose male (-39.52%) and female (-39.87%) animals. <i>60 mg/kg/day</i>: In mid dose male and female animals food consumption in week 4 was decreased by 25.56% and 38.56%, respectively.																																																															
Ophthalmology	No noteworthy findings																																																															
Electrocardiography	<i>200 mg/kg/day</i> : Potentially ziftomenib related decreases in mean heart rate (within the normal range for the canine) were noted after dosing on Days 3 and 24 in high-dose females, prior to dosing on Day 24 in high-dose males, and prior to dosing on Day 24 in low-dose males.																																																															
Hematology	<i>200 mg/kg/day</i>: Statistically significantly decreased reticulocyte count and associated decreases in mean corpuscular volume and red cell distribution with were observed in high dose animals of both sexes. The statistically significantly increased white blood cell count noted for high-dose females was due to increased neutrophil, monocyte, eosinophil, and large unstained cell counts. <table border="1"> <thead> <tr> <th>Parameter (Day 29)</th> <th colspan="4">Male</th> <th colspan="4">Female</th> </tr> <tr> <th>Dose mg/kg/day</th> <th>0</th> <th>20</th> <th>60</th> <th>200</th> <th>0</th> <th>20</th> <th>60</th> <th>200</th> </tr> </thead> <tbody> <tr> <td>Number of animals</td> <td>6</td> <td>4</td> <td>4</td> <td>6</td> <td>6</td> <td>4</td> <td>4</td> <td>6</td> </tr> <tr> <td>Reticulocyte count (10³/μL)</td> <td>40.8</td> <td>-</td> <td>-</td> <td>13.0*</td> <td>34.0</td> <td>-</td> <td>-</td> <td>10.0**</td> </tr> <tr> <td>Mean corpuscular volume (fL)</td> <td>66.4</td> <td>-</td> <td>-</td> <td>65.4</td> <td>68.6</td> <td>-</td> <td>-</td> <td>65.2*</td> </tr> <tr> <td>Red cell distribution width (%)</td> <td>12.7</td> <td>-</td> <td>-</td> <td>11.7**</td> <td>12.4</td> <td>-</td> <td>-</td> <td>11.5*</td> </tr> <tr> <td>White blood cell count</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>7.77</td> <td>-</td> <td>-</td> <td>17.57**</td> </tr> </tbody> </table>	Parameter (Day 29)	Male				Female				Dose mg/kg/day	0	20	60	200	0	20	60	200	Number of animals	6	4	4	6	6	4	4	6	Reticulocyte count (10 ³ /μL)	40.8	-	-	13.0*	34.0	-	-	10.0**	Mean corpuscular volume (fL)	66.4	-	-	65.4	68.6	-	-	65.2*	Red cell distribution width (%)	12.7	-	-	11.7**	12.4	-	-	11.5*	White blood cell count	-	-	-	-	7.77	-	-	17.57**
	Parameter (Day 29)	Male				Female																																																										
	Dose mg/kg/day	0	20	60	200	0	20	60	200																																																							
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	Reticulocyte count (10 ³ /μL)	40.8	-	-	13.0*	34.0	-	-	10.0**																																																							
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	Red cell distribution width (%)	12.7	-	-	11.7**	12.4	-	-	11.5*																																																							
White blood cell count	-	-	-	-	7.77	-	-	17.57**																																																								

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Observations and Results: Main Study Groups									
	(10 ³ /μL)								
	Neutrophil count (10 ³ /μL)	-	-	-	-	4.34	-	-	12.10**
	Monocyte count (10 ³ /μL)	-	-	-	-	0.52			1.33**
	Eosinophil count (10 ³ /μL)	-	-	-	-	0.26	-	-	1.01
	Large unstained cell count (10 ³ /μL)	-	-	-	-	0.02	-	-	0.10*
	Statistically significant Dunnetts test								
Clinical chemistry	≥ 60 mg/kg/day: Effects on serum chemistry parameters were noted for both sexes at the mid- and high-dose levels. Most substantial changes included mild-to-moderate, dose-dependent increases in the activities of several hepatobiliary-associated serum enzymes including ALT, AST, SDH, ALP, and GGT. At the high-dose level, mean serum total bilirubin concentration was minimally increased in females while mean serum cholesterol concentration was mildly decreased in males. Additional noteworthy effects on serum chemistry analytes noted at the end of the dosing phase included mild-to-moderate decreases in serum albumin and total protein concentrations in mid-dose females and in high-dose males and females, decreased serum calcium concentrations in both sexes at the high-dose level (associated with the effect on serum albumin), decreased serum chloride concentrations in 1 male and 3 females at the high-dose level, and dose-dependent decreased serum phosphorus concentrations in both sexes at the mid- and high-dose levels.								
	Parameter Day 29	Male				Female			
	Dose mg/kg/day	0	20	60	200	0	20	60	200
	Number of animals	6	4	4	6	6	4	4	6
	Alanine aminotransferase (U/L)	45	-	293**	281**	34	-	261	426
	Aspartate aminotransferase (U/L)	30	-	57*	82**	30	-	55	139
	Sorbitol	1	-	7	9*	1	-	7	14

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Komzifti (ziftomenib)

Observations and Results: Main Study Groups									
	dehydrogenase (U/L)								
	Alkaline phosphatase (U/L)	100	-	427**	517**	92	-	345	1006
	Gamma-glutamyltransferase (U/L)	1.5	-	6.3	7.8*	2.0	-	5.3	20.3
	Total bilirubin (U/L)	-	-	-	-	0.00	-	-	0.20**
	Total protein (g/dL)	5.3	-	-	4.7**	5.2	-	4.9	4.4**
	Albumin (g/dL)	3.1	-	-	2.5**	3.1	-	2.8*	2.4**
	Albumin/Globulin ratio	1.37	-	-	1.15*	1.40	-	1.33	1.17*
	Cholesterol (mg/dL)	138	-	-	89	-	-	-	-
	Chloride (mEq/L)	112	-	-	107	111	-	-	108
	Calcium (mEq/L)	10.6	-	-	9.9**	10.2	-	-	9.7
	Phosphorus (mEq/L)	6.7	-	5.8*	5.4**	5.9	-	5.4	4.5**
Gross pathology	≥ 60 mg/kg/day: Macroscopic findings were noted in the mid and high dose animals of both sexes in hepatobiliary organs (dilatation of bile duct, white discoloration white foci, gritty content of/in the gall bladder, pale discoloration and green discoloration of the liver), GI tract (dark red foci) and lymphoid tissue (small thymus, spleen).								
Organ weights	200 mg/kg/day: At terminal necropsy in males statistically significantly decreased thymus and epididymis weights and increased liver weight were noted at the high-dose level. ≥ 60 mg/kg/day: In females at the terminal necropsy changes in organ weight included statistically significant decreases in splenic and thymus weights at the mid- and high-dose levels, decreases in kidney and heart weights at the high-dose level, and increased liver weight at the high-dose level.								
Histopathology	At the terminal necropsy, ziftomenib-related microscopic findings involved the hepatobiliary, gastrointestinal, renal, lymphoid, and hematopoietic organs.								

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Observations and Results: Main Study Groups								
The ziftomenib-related findings of basophilic accumulations and increased cellularity of basophilic macrophages involving the liver, bile duct, gallbladder, and intestines noted in mid- and high-dose males and females were considered adverse. In addition, the increased cellularity of vacuolated macrophages within the lymphoid organs and lymphoid depletion of the thymus, Peyer’s patches, and lymph nodes in both sexes at the mid- and high-dose levels and the membranous glomerulopathy were considered adverse.								
Daily Dose mg/kg/day	0		20		60		200	
	M:	F:	M:	F:	M:	F:	M:	F:
Number Examined	6	4	4	4	4	4	4	4
Bile duct								
Accumulation, basophilic	0	0	0	3	2	4	2	2
Mild	0	0	0	1	1	3	1	0
Moderate	0	0	0	2	1	1	1	2
Increased cellularity, basophilic macrophage	0	0	1	1	2	4	2	3
Mild	0	0	1	1	2	3	0	1
Moderate	0	0	0	0	0	1	2	2
Bone marrow, femur								
Increased myeloid to erythroid ratio	0	0	0	0	0	0	4	4
Mild	0	0	0	0	0	0	2	3
Moderate	0	0	0	0	0	0	2	1
Bone marrow, sternum								
Increased myeloid to erythroid ratio	0	0	0	0	0	0	4	4
Mild	0	0	0	0	0	0	2	3
Moderate	0	0	0	0	0	0	2	1
Decreased cellularity	0	0	0	0	1	3	2	3
Minimal	0	0	0	0	1	1	2	0
Mild	0	0	0	0	0	2	0	0
Moderate	0	0	0	0	0	0	0	2
Marked	0	0	0	0	0	0	0	1
Gallbladder								

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Komzifti (ziftomenib)

Observations and Results: Main Study Groups									
	Accumulation, basophilic	0	0	0	0	3	3	4	3
	Moderate	0	0	0	0	2	3	1	1
	Marked	0	0	0	0	1	0	1	2
	Severe	0	0	0	0	0	0	2	0
	Increased cellularity, basophilic macrophage	0	0	0	0	3	3	4	3
	Mild	0	0	0	0	1	0	0	0
	Moderate	0	0	0	0	1	3	1	3
	Marked	0	0	0	0	1	0	3	0
	Kidney								
	Degeneration, tubular	0	0	0	0	0	0	0	2
	Minimal	0	0	0	0	0	0	0	1
	Moderate	0	0	0	0	0	0	0	1
	Regeneration, tubular	0	0	0	0	0	1	2	3
	Minimal	0	0	0	0	0	1	2	1
	Mild	0	0	0	0	0	0	0	1
	Moderate	0	0	0	0	0	0	0	1
	Glomerulopathy, membranous	0	0	0	0	0	0	4	4
	Minimal	0	0	0	0	0	0	4	0
	Mild	0	0	0	0	0	0	0	4
	Accumulation, basophilic, mesangium	0	0	0	0	0	0	4	4
	Minimal	0	0	0	0	0	0	4	2
	Mild	0	0	0	0	0	0	0	2
	Accumulation, basophilic, tubule	0	0	0	0	0	0	4	3
	Minimal	0	0	0	0	0	0	4	1
	Mild	0	0	0	0	0	0	0	2
	Pigment, tubular	0	0	0	0	0	0	2	2
	Minimal	0	0	0	0	0	0	2	2
	Liver								
	Accumulation, basophilic, bile duct	0	0	0	0	4	3	4	4
	Mild	0	0	0	0	1	0	0	0

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Observations and Results: Main Study Groups									
	Moderate	0	0	0	0	1	2	1	0
	Marked	0	0	0	0	2	1	3	4
	Inflammation, mixed cell, periportal	0	0	0	0	4	4	4	4
	Mild	0	0	0	0	2	0	0	1
	Moderate	0	0	0	0	2	4	4	3
	Pigment, macrophage	0	0	0	0	3	2	0	2
	Minimal	0	0	0	0	0	2	0	1
	Mild	0	0	0	0	3	0	0	1
	Increased cellularity, basophilic, macrophage	0	0	0	0	4	4	4	4
	Minimal	0	0	0	0	1	0	0	0
	Mild	0	0	0	0	3	4	2	4
	Marked	0	0	0	0	0	0	2	0
	Lymph node, axillary								
	Depletion, lymphoid	0	0	0	0	2	4	2	4
	Minimal	0	0	0	0	0	3	0	0
	Mild	0	0	0	0	2	1	1	0
	Moderate	0	0	0	0	0	0	1	3
	Marked	0	0	0	0	0	0	0	1
	Increased cellularity, vacuolated macrophage	0	0	0	0	3	3	4	4
	Minimal	0	0	0	0	1	1	0	0
	Mild	0	0	0	0	1	2	3	2
	Moderate	0	0	0	0	1	0	1	2
	Lymph node, mandibular								
	Depletion, lymphoid	0	0	0	0	0	0	3	3
	Mild	0	0	0	0	0	0	1	3
	Moderate	0	0	0	0	0	0	2	0
	Increased cellularity, vacuolated macrophage	0	0	0	0	3	2	3	3
	Minimal	0	0	0	0	2	1	0	0
	Mild	0	0	0	0	1	1	1	0
	Moderate	0	0	0	0	0	0	2	3

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Observations and Results: Main Study Groups									
	Lymph node, mesenteric								
	Depletion, lymphoid	0	0	0	0	1	2	4	4
	Minimal	0	0	0	0	1	2	0	0
	Mild	0	0	0	0	0	0	0	2
	Moderate	0	0	0	0	0	0	4	2
	Increased cellularity, vacuolated macrophage	0	0	0	0	4	4	4	4
	Minimal	0	0	0	0	1	0	0	0
	Mild	0	0	0	0	2	3	0	0
	Moderate	0	0	0	0	1	1	1	3
	Marked	0	0	0	0	0	0	3	1
	Increased cellularity, basophilic macrophage	0	0	0	0	0	0	1	0
	Mild	0	0	0	0	0	0	1	0
	Peyer's patch								
	Depletion, lymphoid	0	0	0	0	2	2	4	4
	Minimal	0	0	0	0	2	2	0	0
	Mild	0	0	0	0	0	0	0	1
	Moderate	0	0	0	0	0	0	2	2
	Marked	0	0	0	0	0	0	2	1
	Increased cellularity, vacuolated macrophage	0	0	0	0	4	4	4	4
	Minimal	0	0	0	0	1	0	0	0
	Mild	0	0	0	0	2	3	1	0
	Moderate	0	0	0	0	1	1	0	2
	Marked	0	0	0	0	0	0	3	2
	Small intestine, duodenum								
	Increased cellularity, basophilic macrophage	0	0	0	0	0	0	0	3
	Minimal	0	0	0	0	0	0	0	2
	Mild	0	0	0	0	0	0	0	1
	Small intestine, ileum								

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Observations and Results: Main Study Groups									
	Increased cellularity, basophilic macrophage	0	0	0	0	0	0	4	4
	Minimal	0	0	0	0	0	0	1	0
	Mild	0	0	0	0	0	0	2	2
	Moderate	0	0	0	0	0	0	1	2
	Small intestine, jejunum								
	Increased cellularity, basophilic macrophage	0	0	0	0	1	1	4	4
	Minimal	0	0	0	0	1	0	0	0
	Mild	0	0	0	0	0	0	2	2
	Moderate	0	0	0	0	0	1	2	2
	Spleen								
	Depletion, lymphoid	0	0	0	0	0	0	4	3
	Mild	0	0	0	0	0	0	2	3
	Marked	0	0	0	0	0	0	2	0
	Increased cellularity, vacuolated macrophage, red pulp	0	0	0	0	2	2	4	4
	Mild	0	0	0	0	1	0	0	0
	Moderate	0	0	0	0	1	2	4	4
	Increased cellularity, vacuolated macrophage, white pulp	0	0	1	0	3	4	4	4
	Minimal	0	0	1	0	0	1	0	0
	Mild	0	0	0	0	3	3	0	0
	Moderate	0	0	0	0	0	0	4	4
	Stomach								
	Increased cellularity, vacuolated macrophage	0	0	0	0	1	3	4	3
	Minimal	0	0	0	0	1	0	0	1
	Mild	0	0	0	0	0	3	1	2
	Moderate	0	0	0	0	0	0	3	0
	Thymus								
	Depletion, lymphoid	0	0	0	0	2	3	3	4

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Observations and Results: Main Study Groups																														
	Mild	0	0	0	0	1	0	0	0																					
	Moderate	0	0	0	0	1	0	0	0																					
	Marked	0	0	0	0	0	3	1	0																					
Other relevant evaluations	Transmission electron microscopy (TEM) revealed an increased numbers and/or larger lysosomes containing phospholipid- like material (in myelinoid aggregates, lamellar, and/or multivesicular bodies) within the cytoplasm of hepatocytes and Kupffer cells of ziftomenib-treated dogs when compared with lysosomes of vehicle-treated control animals. These findings persisted at the end of the recovery period, with somewhat decreased size and incidence of lysosomes containing phospholipid material within hepatocytes and Kupffer cells indicating partial recovery (ie, fewer lysosomes containing nascent phospholipid material). Taken together, the increased incidence and magnitude of lysosomal accumulation of phospholipid material in high-dose animals are consistent with a diagnosis of phospholipidosis.																													
Toxicokinetics	Systemic exposure to ziftomenib and KO-516 (metabolite) was independent of sex. Mean C_{max} and AUC_{0-24h} values for ziftomenib increased with increasing dose in an approximately dose-proportional manner on Day 1. On Day 28, mean C_{max} values for ziftomenib increased with increasing dose in a less-than-dose-proportional manner while AUC_{0-24h} values for ziftomenib increased with increasing dose in an approximately dose-proportional manner. Mean C_{max} and AUC_{0-24h} values for KO-516 increased with increasing dose in an approximately dose-proportional manner on Day 1 and in a less-than-dose-proportional manner on Day 28. Systemic exposure to ziftomenib and KO-516 generally appeared to increase following repeated administration of ziftomenib at 20 and 60 mg/kg/day with no change at 200 mg/kg/day. Systemic exposure (AUC_{0-24h}) to KO-516 was approximately 19% to 35% of the systemic exposure to ziftomenib. Combined-sex systemic exposure (C_{max} and AUC_{0-24h}) to ziftomenib at the HNSTD (60 mg/kg/day) on Day 28 was 1150 ng/mL and 22,500 ng*hr/mL, respectively. Corresponding values for the KO-516 metabolite were 290 ng/mL and 5600 ng*hr/mL, respectively. Overview of Toxicokinetic Data <table border="1"> <thead> <tr> <th rowspan="2">Ziftomenib (mg/kg/day)</th> <th rowspan="2">Day</th> <th colspan="2">Ziftomenib^a</th> <th colspan="2">KO-516^a</th> </tr> <tr> <th>C_{max} (ng/mL)</th> <th>AUC_{0-24h} (ng*hr/mL)</th> <th>C_{max} (ng/mL)</th> <th>AUC_{0-24h} (ng*hr/mL)</th> </tr> </thead> <tbody> <tr> <td rowspan="2">20</td> <td>1</td> <td>220</td> <td>3150</td> <td>72.3</td> <td>1090</td> </tr> <tr> <td>28</td> <td>343</td> <td>5310</td> <td>85.5</td> <td>1680</td> </tr> </tbody> </table>									Ziftomenib (mg/kg/day)	Day	Ziftomenib ^a		KO-516 ^a		C _{max} (ng/mL)	AUC _{0-24h} (ng*hr/mL)	C _{max} (ng/mL)	AUC _{0-24h} (ng*hr/mL)	20	1	220	3150	72.3	1090	28	343	5310	85.5	1680
Ziftomenib (mg/kg/day)	Day	Ziftomenib ^a		KO-516 ^a																										
		C _{max} (ng/mL)	AUC _{0-24h} (ng*hr/mL)	C _{max} (ng/mL)	AUC _{0-24h} (ng*hr/mL)																									
20	1	220	3150	72.3	1090																									
	28	343	5310	85.5	1680																									

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Komzifti (ziftomenib)

Observations and Results: Main Study Groups						
	60	1	1190	16,400	262	4150
		28	1150	22,500	290	5600
	200	1	3060	43,300	512	8040
		28	2000	39,500	393	7430
Abbreviations: AUC=area under the plasma concentration-time curve; AUC_{0-24h}=area under the plasma concentration-time curve from time 0 to 24 hours; C_{max}=maximum plasma concentration. ^a Systemic exposure to ziftomenib and KO-516 was independent of sex; therefore, data are reported as combined-sex values (mean ± standard deviation).						

Observations and Results: Recovery Groups Day 56/57	
Due to the unscheduled deaths of 2 males in Group 4, all surviving Group 4 males were assigned to the terminal necropsy; all males in the vehicle control group were assigned to the terminal necropsy due to no assessment of recovery in the males. Recovery data are only available for the female anyimals.	
Body weight	Full recovery was observed Day 56/57 in high dose females.
Food consumption	
Hematology and Coagulation	
Clinical chemistry	Findings in one high-dose (200 mg/kg/day) female included progression in elevated ALP and GGT activities, persistently increased SDH activity, persistently decreased serum albumin concentration, partial recovery in ALT, and full recovery of elevated AST activity and serum total bilirubin concentration. In the other high-dose female, full recovery of the increased AST activity and total bilirubin concentration were noted, with partial recovery of the increases in ALT, SDH, ALP, and GGT noted at the end of the dosing phase. However, in this female, there was further progression of the decreased serum albumin concentration. The decreases in serum calcium concentration noted for both females at the terminal collection had progressed in both animals by the end of the recovery phase. Resolution of the decreased serum chloride and phosphorus concentrations was noted female while the decreases persisted in the other recovery female.
Gross pathology	Small thymus was observed in the two female animals.

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Komzifti (ziftomenib)

Organ weights	Lower thymus weights noted in the two female animals.
Histopathology	The persistence of basophilic accumulations, increased cellularity of basophilic macrophages, vacuolated macrophages, lymphoid depletion, and membranous glomerulopathy and the development of widespread intracytoplasmic pigment within macrophages, hepatocytes, and renal tubular epithelium of high-dose females indicate a lack of the reversibility of these lesions following cessation of dosing.

A 13-Week (Twice Daily) Oral Gavage Toxicity and Toxicokinetic Study of KO-539 in Dogs with a 28-Day Recovery Period/ Study No. KO-TOX-0013/ Section 3.6 of Module 2.6.6, Section 7.2.2 of Module 2.6.7

Key Drug-related Adverse Findings

- Microscopic findings considered adverse at 60 mg/kg/day were noted in the hepatobiliary and lymphoid systems in both sexes with correlating effects on clinical pathology analytes. As these findings persisted in 60 mg/kg/day animals at the end of the 4-week treatment-free recovery period, they were considered to represent severe toxicity.
- GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 mg/kg bid (0 mg/kg/day), 3 mg/kg bid (6 mg/kg/day), 10 mg/kg bid (20 mg/kg/day), and 30 mg/kg bid (60 mg/kg/day). Daily doses were administered at least 6 hours, but not more than 7 hours, apart.
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) in reverse osmosis deionized water with 3.0 molar equivalent (b) (4) pH (b) (4) solution.
Species/Strain:	Dog, Beagle
Number/Sex/Group:	4 animals/sex (vehicle and high dose group 2 animals/group)
Age:	Approximately 5-6 months
Satellite groups:	None

Observations and Results: Main Study Groups

Parameters	Major findings
Mortality	All animals survived until scheduled termination.

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Komzifti (ziftomenib)

Clinical signs	60 mg/kg/day: thin, salivation, soft feces, mucoid feces, activity decreased, tremors, hunched posture, and abdominal distension ≥20 mg/kg/day: liquid feces and material present (white and/or foamy, liquid [clear, green, red, white, brown, or yellow], and mucoid)								
Body weight	60 mg/kg/day: on Day 91 body weight was statistically significantly decreased in male (-11.83%) and female (-21.54%) animals								
Food consumption	60 mg/kg/day: In week 13 food consumption was statistically significantly decreased in male (-20.78%) and female (-34.65%) animals.								
Ophthalmology	No noteworthy findings								
Electrocardiography	No noteworthy findings								
Hematology and Coagulation	60 mg/kg/day: Statistically significant leukocyte changes were noted in both sexes including increases in white blood cells, neutrophils, monocytes and large unstained cells and decreases in red blood cells, hemoglobin hematocrit, mean corpuscular hemoglobin, and red blood cell distribution. ≥20 mg/kg/day: Red blood cells, hemoglobin, and hematocrit were statistically significantly decreased in both sexes								
	Daily Dose (mg/kg/day)	0		6		20		60	
	No. of Animals	M:6	F:6	M:4	F:4	M:4	F:4	M:6	F:6
	White blood cells (10 ³ /μL)	7.677	8.698	9.763	9.963	11.598	11.180	13.020**	17.760**
	Neutrophils (10 ³ /μL)	4.035	5.142	6.000	5.843	7.098*	7.040	9.167**	12.810**
	Monocytes (10 ³ /μL)	0.502	0.463	0.600	0.423	0.730	0.605	1.042	1.240**
	Large unstained cells (10 ³ /μL)	0.037	0.042	0.048	0.075	0.113*	0.088	0.132**	0.150**
	Red blood cells (10 ⁶ /μL)	6.487	6.882	6.245	6.365	5.670**	5.940*	4.868**	4.752**
	Hemoglobin (g/dL)	14.55	15.25	14.00	14.30	12.60*	13.35*	10.35**	9.93**
	Hematocrit (%)	44.12	46.07	42.75	43.40	38.45**	40.38*	32.00**	30.88**
	Mean corpuscular hemoglobin (pg)	22.43	22.18	22.40	22.50	22.28	22.45	21.27*	20.95*
	Mean corpuscular hemoglobin concentration (g/dL)	33.02	33.12	32.73	33.00	32.80	33.05	32.28	32.22*
Red blood cell	12.67	12.58	12.30	12.30	12.13	11.75	11.20**	11.42**	

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Komzifti (ziftomenib)

	distribution width (%)								
	Coagulation								
	Fibrinogen (mg/dL)	212.3	192.5	237.3	167.5	247.8	188.0	471.0**	487.0**
Clinical chemistry	60 mg/kg/day: Findings included significant increases in mean serum AST, ALT, ALP, and GGT activities; mean serum total bilirubin concentration; decreased mean serum albumin concentration; increased mean serum globulin concentration; and decreased mean serum calcium concentration; statistically significant decreases in mean serum phosphorus and potassium concentrations.								
	Daily Dose (mg/kg/day)	0		6		20		60	
	No. of Animals	M:6	F:6	M:4	F:4	M:4	F:4	M:6	F:6
	AST (U/L)	32.7	29.8	29.3	27.3	29.8	26.0	88.0*	115.5*
	ALT(U/L)	37.7	39.3	34.3	38.5	41.3	38.3	239.7*	288.5*
	ALP (U/L)	84.3	76.2	94.5	98.0	81.3	65.0	1396.3**	2035.0*
	GGT (U/L)	0.3	0.0	0.0	0.3	0.0	0.0	7.0	9.5*
	Total bilirubin (mg/dL)	0.042	0.028	0.028	0.043	0.023	0.043	0.105	0.147
	Total protein (g/dL)	5.40	5.30	5.13	5.38	5.03	5.13	4.83**	4.45*
	Albumin (g/dL)	3.17	3.28	3.13	3.28	3.00	3.15	2.32**	2.02**
	Globulin (g/dL)	2.23	2.02	2.00	2.10	2.03	1.98	2.52	2.43*
	Albumin/globulin (ratio)	1.43	1.65	1.58	1.58	1.48	1.60	0.93**	0.85**
	Calcium (mg/dL)	10.35	10.17	10.08	10.18	10.13	10.13	9.32**	8.87**
	Phosphorus (mg/dL)	5.47	4.67	5.58	5.35	5.80	4.90	4.70*	4.90
Potassium (mEq/L)	4.78	4.57	4.86	4.80	4.67	4.39	4.33*	4.34	
Cholesterol (mg/dL)	123.8	134.7	127.8	136.0	98.3	110.5	97.2*	77.0**	
Gross pathology	60 mg/kg/day: pale discoloration (4/4 M&F) and an irregular surface of the liver (1/4 F); pale yellow fluid accumulation in the abdominal and thoracic body cavities (1/1 F); dilatation of the gallbladder (2/4 M; 4/4 F) and bile duct (1/1 M; 2/2 F); abnormal content (1/4 M; 2/4 F), and pale discoloration (2/4 M; 4/4 F) in the gallbladder; enlargement and varying degrees of discoloration the mesenteric lymph nodes; small prostate (1/4 M); and pale discoloration in multiple organs								
Organ weights	60 mg/kg/day: Statistically significantly increased (vs control) mean organ weight values were noted for the liver/gallbladder, kidney, and adrenal gland; and statistically significantly decreased (vs control) mean organ weight values for the thymus, prostate, and testes.								

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Komzifti (ziftomenib)

Histopathology	<i>60 mg/kg/day:</i> Target organs included the hepatobiliary system (liver, gallbladder, and bile duct), adrenal gland, lymphoid tissues (mandibular and mesenteric lymph nodes, gut-associated lymphoid tissue [GALT], spleen, sternal bone marrow, and thymus), and the reproductive tracts of males (testis, epididymis, and prostate) and females (ovaries) in dogs. Findings considered adverse were noted in the hepatobiliary system and lymphoid organs of dogs.									
	Daily Dose (mg/kg/day)		0		6		20		60	
	No. of Animals		M:6	F:6	M:4	F:4	M:4	F:4	M:6	F:6
	Liver (no. examined)		4	4	4	4	4	4	4	4
	Hyperplasia; biliary		0	0	0	0	3	0	4	4
	Minimal		-	-	-	-	2	-	0	0
	Mild		-	-	-	-	1	-	0	1
	Moderate		-	-	-	-	0	-	1	2
	Marked		-	-	-	-	0	-	3	1
	Cholestasis		0	0	0	0	1	0	4	4
	Minimal		-	-	-	-	1	-	0	0
	Mild		-	-	-	-	0	-	2	2
	Moderate		-	-	-	-	0	-	2	2
	Inflammation, mixed cell; periportal		0	0	0	0	2	0	4	4
	Minimal		-	-	-	-	2	-	2	2
	Mild		-	-	-	-	0	-	2	2
	Vacuolation; hepatocellular		0	0	0	0	0	0	3	4
	Moderate		-	-	-	-	-	-	2	3
	Marked		-	-	-	-	-	-	1	1
	Cellularity, increased; basophilic, macrophage		0	0	0	0	0	0	2	4
	Mild		-	-	-	-	-	-	2	3
	Moderate		-	-	-	-	-	-	0	1
	Pigment; macrophage		0	0	0	0	2	0	2	4
Minimal		-	-	-	-	2	-	0	0	
Mild		-	-	-	-	0	-	2	3	

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Komzifti (ziftomenib)

Moderate	-	-	-	-	0	-	0	1
Accumulation; basophilic, bile duct	0	0	0	0	3	0	4	4
Minimal	-	-	-	-	3	-	1	1
Mild	-	-	-	-	0	-	3	3
Gallbladder (no. examined)	4	4	4	4	4	4	4	4
Accumulation; basophilic	0	0	0	0	0	0	4	4
Minimal	-	-	-	-	-	-	1	3
Mild	-	-	-	-	-	-	3	1
Cellularity, increased; basophilic, macrophage	0	0	0	0	0	0	4	4
Minimal	-	-	-	-	-	-	1	3
Mild	-	-	-	-	-	-	3	1
Duct, bile (no. examined)	0	0	0	0	0	0	1	2
Accumulation; basophilic	-	-	-	-	-	-	1	1
Minimal	-	-	-	-	-	-	1	1
Cellularity, increased; basophilic, macrophage	0	0	0	0	0	0	1	2
Minimal	-	-	-	-	-	-	0	2
Mild	-	-	-	-	-	-	1	0
Lymph node, mandibular (no. examined)	4	4	4	4	4	4	4	4
Cellularity, decreased, lymphocyte	0	0	0	0	0	1	4	2
Minimal	-	-	-	-	-	1	4	2
Increased cellularity, vacuolated macrophage	0	0	0	0	0	0	4	3

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Komzifti (ziftomenib)

	Minimal	-	-	-	-	-	-	4	3
	Increased cellularity, pigmented macrophage	0	0	0	1	0	1	4	3
	Minimal	-	-	-	1	-	1	4	3
	Congestion	0	0	1	0	0	0	0	1
	Mild	-	-	1	-	-	-	-	1
	Lymph node, mesenteric (no. examined)	4	4	4	4	4	4	4	4
	Cellularity, decreased; lymphocyte	0	0	0	0	2	1	4	4
	Minimal	-	-	-	-	2	1	4	1
	Mild	-	-	-	-	0	0	0	3
	Increased cellularity, vacuolated macrophage	0	0	0	0	0	3	4	4
	Minimal	-	-	-	-	-	2	2	1
	Mild	-	-	-	-	-	1	2	2
	Moderate	-	-	-	-	-	0	0	1
	Increased cellularity, pigmented macrophage	0	2	0	1	0	4	1	4
	Minimal	-	2	-	1	-	4	0	1
	Mild	-	0	-	0	-	0	1	3
	Congestion	0	2	1	4	3	4	4	4
	Minimal	-	0	0	3	2	1	1	0
	Mild	-	2	1	1	1	3	2	2
	Moderate	-	0	0	0	0	0	1	2
	GALT (no. examined)	4	4	4	4	4	4	4	4
	Cellularity, decreased; lymphocyte	0	0	0	0	0	0	4	3
	Minimal	-	-	-	-	-	-	1	3

Version date: March 1, 2024 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Komzifti (ziftomenib)

	Mild	-	-	-	-	-	-	3	0
	Increased cellularity, vacuolated macrophage	0	0	0	0	3	0	3	4
	Minimal	-	-	-	-	3	-	0	1
	Mild	-	-	-	-	0	-	3	3
	Spleen (no. examined)	4	4	4	4	4	4	4	4
	Cellularity, decreased; lymphocyte	0	0	0	0	1	0	3	4
	Minimal	-	-	-	-	1	-	2	4
	Mild	-	-	-	-	0	-	1	0
	Increased cellularity, vacuolated macrophage	0	0	0	0	0	0	4	4
	Minimal	-	-	-	-	-	-	2	0
	Mild	-	-	-	-	-	-	2	4
	Thymus (no. examined)	4	4	4	4	4	4	4	4
	Cellularity, decreased; lymphocyte	0	0	0	0	0	0	3	4
	Mild	-	-	-	-	-	-	1	1
	Moderate	-	-	-	-	-	-	1	2
	Marked	-	-	-	-	-	-	1	1
	Testis (no. examined)	4	N/A	4	N/A	4	N/A	4	N/A
	Vacuolation; seminiferous tubule	0	N/A	0	N/A	0	N/A	4	N/A
	Mild	-	N/A	-	N/A	-	N/A	4	N/A
	Epididymis (no. examined)	4	N/A	4	N/A	4	N/A	4	N/A
	Decreased sperm, luminal	0	N/A	0	N/A	4	N/A	4	N/A
	Minimal	-	N/A	-	N/A	3	N/A	0	N/A
	Mild	-	N/A	-	N/A	1	N/A	0	N/A

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Komzifti (ziftomenib)

	Marked	-	N/A	-	N/A	0	N/A	4	N/A																													
	Prostate (no. examined)	4	N/A	4	N/A	4	N/A	4	N/A																													
	Immaturity	0	N/A	0	N/A	0	N/A	3	N/A																													
	Ovary (no. examined)	N/A	4	N/A	4	N/A	4	N/A	4																													
	Immaturity; follicle	N/A	0	N/A	0	N/A	0	N/A	4																													
Other relevant evaluations	None.																																					
Toxicokinetics	Systemic exposure to ziftomenib and its 2 metabolites, KO-516 and KO-739, was generally similar between males and females. KO-516-to-ziftomenib ratios for overall daily exposure (in terms of AUC_{tlast}) were 0.258 to 0.405 on both evaluation days. KO-739-to-ziftomenib ratios for overall daily exposure (AUC_{tlast}) were 0.913 to 1.57 on Day 1 and 1.79 to 6.25 on Day 91. Exposure (C_{max} and AUC_{tlast}) to all 3 analytes generally increased with increasing dose from 6 to 60 mg/kg/day in a greater-than-dose-proportional manner in both sexes on both Days 1 and 91. Exposure to KO-516 was nearly or approximately dose proportional on Day 91, in terms of C_{max} in males and both C_{max} and AUC_{tlast} in females. There was no meaningful accumulation of ziftomenib or KO-516 in plasma on Day 91 relative to Day 1. However, accumulation of KO-739 in plasma was noted in both sexes on Day 91, as indicated by mean accumulation ratios ranging from 2.04 to 5.78. Systemic exposure (mean C_{max} and AUC_{tlast}) to ziftomenib at the NOAEL/HNSTD (20 mg/kg/day) on Day 91 was 274 ng/mL and 5100 ng*hr/mL, respectively, in males and 271 ng/mL and 4930 ng*hr/mL, respectively, in females. Corresponding values for the KO-516 metabolite were 104 ng/mL and 1740 ng*hr/mL, respectively, in males and 90.2 ng/mL and 1550 ng*hr/mL, respectively, in females. Corresponding values for the KO-739 metabolite were 1510 ng/mL and 22,000 ng*hr/mL, respectively, in males and 1630 ng/mL and 24,300 ng*hr/mL, respectively, in females. <table border="1"> <thead> <tr> <th>Analyte</th> <th>Day</th> <th>Ziftomenib (mg/kg/day)</th> <th>Sex</th> <th>C_{max} (ng/mL)^a</th> <th>AUC_{tlast} (ng*hr/mL)^a</th> </tr> </thead> <tbody> <tr> <td rowspan="6">Ziftomenib</td> <td rowspan="6">1</td> <td rowspan="2">6</td> <td>Males</td> <td>57.3</td> <td>695</td> </tr> <tr> <td>Females</td> <td>59.5</td> <td>714</td> </tr> <tr> <td rowspan="2">20</td> <td>Males</td> <td>294</td> <td>3960</td> </tr> <tr> <td>Females</td> <td>294</td> <td>3660</td> </tr> <tr> <td rowspan="2">60</td> <td>Males</td> <td>1420</td> <td>18,700</td> </tr> <tr> <td>Females</td> <td>1110</td> <td>15,800</td> </tr> </tbody> </table>									Analyte	Day	Ziftomenib (mg/kg/day)	Sex	C _{max} (ng/mL) ^a	AUC _{tlast} (ng*hr/mL) ^a	Ziftomenib	1	6	Males	57.3	695	Females	59.5	714	20	Males	294	3960	Females	294	3660	60	Males	1420	18,700	Females	1110	15,800
Analyte	Day	Ziftomenib (mg/kg/day)	Sex	C _{max} (ng/mL) ^a	AUC _{tlast} (ng*hr/mL) ^a																																	
Ziftomenib	1	6	Males	57.3	695																																	
			Females	59.5	714																																	
		20	Males	294	3960																																	
			Females	294	3660																																	
		60	Males	1420	18,700																																	
			Females	1110	15,800																																	

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		91	6	Males	33.7	699		
				Females	49.1	853		
				20	20	Males	274	5100
						Females	271	4930
				60	60	Males	726	15,300
						Females	780	15,300
	KO-516	1		6	Males	17.7	252	
					Females	16.9	257	
				20	Males	93.1	1500	
					Females	78.4	1180	
				60	Males	365	5730	
					Females	342	5290	
		91		6	Males	14.9	283	
					Females	16.9	308	
				20	Males	104	1740	
					Females	90.2	1550	
				60	Males	184	4340	
					Females	182	3940	
	KO-739	1		6	Males	42.9	634	
					Females	47.0	694	
				20	Males	245	4090	
					Females	314	5060	
				60	Males	1870	24,600	
					Females	2060	24,900	
91			6	Males	73.3	1250		
				Females	96.8	1590		
			20	Males	1510	22,000		
				Females	1630	24,300		
			60	Males	4900	95,700		
				Females	4650	88,300		
Abbreviations: AUC=area under the plasma concentration-time curve; AUC _{tlast} =area under the plasma concentration-time curve from time 0 to the last quantifiable timepoint; C _{max} =maximum plasma concentration. ^a Data are reported as mean ± standard deviation.								
Observations and Results: Recovery Groups Day 120								
Clinical Signs	Ziftomenib-related clinical observations resolved by Day 97 (females) or Day 113 (males).							
Body weight								

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Komzifti (ziftomenib)

Food consumption	Effects were partially (body weight/body weight gain) or fully (food consumption) recovered.
Hematology and Coagulation	The decreases in hemoglobin, hematocrit, MCH, and MCHC persisted in both sexes, with partial reversibility of RBC counts in both sexes and MCV in females.
Clinical chemistry	The increased ALP persisted in females, with partial reversibility of ALP in males and ALT in both sexes. The decreased ALB had partially reversed in both sexes while the increased GLOB persisted. Decreased mean serum cholesterol (CHOL) showed partial reversibility.
Gross pathology	Macroscopic findings included pale, green discoloration of the liver; abnormal content, discoloration, and dilatation of the gallbladder; and green discoloration and enlargement of the mesenteric lymph nodes.
Histopathology	Adverse microscopic findings in the hepatobiliary and lymphoid systems persisted

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment. Pivotal reports previously reviewed are summarized below or described below if not previously reviewed.

In the previously reviewed 28-day repeat-dose toxicology study in mice (study number 00275510, reviewed under IND 142028), animals were treated twice daily by oral gavage with ziftomenib at doses 40, 120, or 400 mg/kg/day. The high-dose was poorly tolerated, and animals were given a 3-day dosing holiday due to signs of excessive toxicity. Dosing was resumed at 200 mg/kg/day. There were 3 unscheduled deaths in the high-dose male group that occurred on Days 17-22. All animals were euthanized in extremis due to adverse body weight loss and declining clinical condition. Animals presented with clinical signs of severe dehydration, decreased activity, and pale skin. The primary histological findings were macrophage infiltration and vacuolation of the liver, lung, and lymphoid tissues. Additionally, there was an unscheduled euthanasia of a female in the mid-dose group that was dehydrated with decreased activity, pale skin, and was cold to the touch, but no clear cause morbidity was identified. Gross pathology revealed discoloration in the liver (green) in animals treated with ≥ 120 mg/kg/day, which correlated to other signs of liver toxicity, including increased transaminases, sorbitol dehydrogenase, and bilirubin, increased liver weight, and macrophage infiltration. Microscopic findings of cellular infiltration and vacuolation were observed in the lung and lymphoid tissues, and minimal to moderate cytoplasmic rarefaction was observed in the kidney. A decrease in erythrocyte counts was also observed with associated decreases in hematocrit and hemoglobin.

Observations made during FDA's assessment of the 13-week toxicology study in mice, some of which were not captured by the Applicant, are included in the Tables below. Seven animals from the test article groups were found dead or euthanized in extremis. Of these, malignant lymphoma was noted microscopically in the lymph nodes, thymus, bone marrow, heart, kidney, liver, lung,

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ovary, spleen, and stomach tissue in one mid-dose animal and was determined to be the cause of morbidity, with ziftomenib likely being responsible given the incidences of hyperplasia noted in the test article dose groups. For the animals that were euthanized on schedule, mid- and high-dose animals had elevated body weights and weight gains. These observations did not correlate with food consumption. Notable hematology findings were reversible and included basophil, large unstained cell, monocyte, and neutrophil counts. Notable clinical chemistry findings included elevated alanine and aspartate aminotransferases, bilirubin, creatine kinase, and triglycerides. These levels remained elevated at the end of the recovery period. Adrenal gland, pituitary gland, kidney, liver, spleen, and thymus weights increased and did not resolve notably by the end of the recovery period. Macroscopic findings were most notable in the liver, with reversible red discoloration. Microscopic findings in the liver included pigmentation in the high-dose groups and dose-dependent hypertrophy. Reversible dose-dependent hyperplasia was noted in the adrenal glands.

FDA Table 5. Summary of Body Weight Findings

Study Day	Unit	Group (mg/kg/day)							
		Male				Female			
		0	12	40	120	0	12	40	120
92	grams	35.3	1.73%	2.58%	9.08%	27.9	5.48%	9.72%	22.94%
120		37.0			9.59%	30.9			10.77%

Test article findings are the percent of control levels

FDA Table 6. Summary of Hematology Findings

Test	Unit	Group (mg/kg/day)							
		Male				Female			
		0	12	40	120	0	12	40	120
Basophils	10 ⁹ /L	0.01	-34.37%	-65.00%	-41.67%	0.00	540.00%	471.43%	380.00%
Eosinophils		0.15	-11.67%	-14.15%	-39.10%	0.09	36.34%	15.90%	-16.62%
Erythrocytes	10 ¹² /L	9.88	-4.23%	-10.76%	-14.15%	9.87	-3.76%	-9.89%	-14.47%
Hematocrit	%	50.3	-1.25%	-10.26%	-14.76%	51.9	-3.73%	-8.43%	-14.40%
Hemoglobin	g/dL	14.6	-1.70%	-9.64%	-16.89%	15.2	-3.31%	-8.42%	-14.26%
Large Unstained Cells	10 ⁹ /L	0.02	-24.17%	-34.67%	50.37%	0.01	240.00%	300.00%	280.00%
Monocytes		0.16	-23.91%	-39.74%	54.88%	0.07	8.57%	16.33%	107.14%
Neutrophils		1.04	-41.91%	-36.56%	-10.22%	0.54	32.10%	30.39%	55.01%

Test article findings are the percent of control levels

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FDA Table 7. Summary of Clinical Chemistry Findings

Test	Unit	Group (mg/kg/day)							
		Male				Female			
		0	12	40	120	0	12	40	120
Alanine Aminotransferase	U/L	93	57.34%	59.16%	200.54%	135	9.21%	53.43%	172.68%
Alkaline Phosphatase		66	11.25%	-1.37%	9.42%	95	-1.69%	-0.97%	29.36%
Aspartate Aminotransferase		94	48.62%	28.72%	85.32%	124	7.98%	69.44%	107.10%
Bilirubin	mg/dL	0.09	1.06%	31.91%	57.45%	0.05	16.98%	9.01%	118.87%
Creatine Kinase	U/L	384	184.31%	97.78%	10.53%	156	27.19%	31.87%	43.25%
Creatinine	mg/dL	0.1	-9.09%	0.00%	0.00%	0.1	0.00%	11.11%	27.27%
Triglycerides		122	7.40%	-11.59%	31.47%	82	20.37%	20.33%	23.29%

Test article findings are the percent of control levels

FDA Table 8. Summary of Organ Weight Findings

Organ/ Tissue	Test	Units	Group (mg/kg/day)							
			Male				Female			
			0	12	40	120	0	12	40	120
GLAND, ADRENAL	Organ/Body Weight	%	0.01	-5.87%	7.16%	35.61%	0.03	-7.90%	-3.81%	24.83%
	Organ/Brain Weight		0.88	-2.74%	13.72%	55.70%	1.87	-0.62%	9.50%	56.94%
	Weight	g	0.0	-4.65%	9.80%	47.57%	0.0	-2.59%	5.95%	53.70%
GLAND, PITUITARY	Organ/Body Weight	%	0.01	0.63%	-0.84%	13.67%	0.01	-6.19%	14.47%	34.49%
	Organ/Brain Weight		0.38	3.87%	4.35%	29.84%	0.53	0.02%	29.41%	66.72%
	Weight	g	0.0	2.84%	1.75%	23.88%	0.0	-1.57%	25.06%	63.67%
HEART	Organ/Body Weight	%	0.47	-2.22%	6.45%	8.12%	0.48	-2.28%	-1.51%	0.57%
	Organ/Brain Weight		34.16	1.41%	12.87%	24.22%	27.36	5.44%	11.96%	25.58%
	Weight	g	0	-0.09%	9.68%	18.23%	0	3.63%	8.23%	23.32%
KIDNEY	Organ/Body Weight	%	1.29	0.37%	9.40%	12.54%	1.17	-2.40%	-1.52%	8.91%
	Organ/Brain Weight		94.15	4.31%	16.30%	29.18%	66.12	5.18%	11.95%	36.98%

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Organ/ Tissue	Test	Units	Group (mg/kg/day)							
			Male				Female			
			0	12	40	120	0	12	40	120
	Weight	g	0	2.79%	13.11%	22.90%	0	3.12%	8.21%	34.13%
LIVER/ GALLBLADDER	Organ/Body Weight	%	4.61	1.44%	2.60%	30.28%	4.74	-0.43%	2.56%	34.89%
	Organ/Brain Weight		337.77	4.68%	8.28%	48.80%	267.97	7.04%	16.62%	69.17%
	Weight	g	2	3.19%	5.36%	41.91%	1	4.92%	12.66%	65.61%
SPLEEN	Organ/Body Weight	%	0.22	-5.54%	-0.95%	30.86%	0.34	-10.04%	-2.17%	16.38%
	Organ/Brain Weight		15.98	-2.28%	4.64%	49.54%	18.91	-2.79%	11.53%	46.12%
	Weight	g	0	-3.77%	1.93%	42.73%	0	-5.12%	7.67%	42.88%
THYMUS	Organ/Body Weight	%	0.07	5.00%	17.03%	10.90%	0.12	-7.29%	15.11%	24.12%
	Organ/Brain Weight		5.05	8.35%	23.59%	26.86%	6.78	0.27%	30.88%	54.47%
	Weight	g	0	6.70%	20.03%	20.44%	0	-1.95%	27.10%	52.77%
TESTIS	Organ/Body Weight	%	0.6932	-0.39%	-2.93%	-7.97%				
	Organ/Brain Weight		50.27128	3.53%	3.33%	6%				
	Weight	g	0.243	1.7%	0.12%	0.57%				

Test article findings are the percent of control levels

FDA Table 9. Summary of Macroscopic Findings

Organ/ Tissue	Finding		Group (mg/kg/day)							
			Male				Female			
			0	12	40	120	0	12	40	120
LIVER		# Animals Examined	20	20	20	20	20	20	21	20
	Discoloration, dark					16				12
		Total				16				12
	Focus, dark			1						
		Total		1						

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FDA Table 10. Summary of Microscopic Findings

Organ/ Tissue	Finding	Severity	Group (mg/kg/day)								
			Male				Female				
			0	12	40	120	0	12	40	120	
LIVER		# Animals Examined	11	10	10	10	10	10	11	10	
	CYTOPLASMIC ALTERATION/ PIGMENT	1 OF 5				4				1	
		2 OF 5				2				6	
		3 OF 5				4				3	
		Total				10				10	
	HYPERTROPHY	1 OF 5		3	2	2					7
		2 OF 5			5	4					2
		3 OF 5			1	3					
		Total		3	8	9					9
	INFILTRATE	1 OF 5	3	1		3	2	2	2	2	2
		Total	3	1		3	2	2	2	2	2
	LYMPHOMA, MALIGNANT									1	
		Total								1	
	NECROSIS	1 OF 5						1			
Total							1				
GLAND, ADRENAL		# Animals Examined	11	10	9	10	10	10	11	10	
	HEMORRHAGE	2 OF 5							1		
		Total							1		
	HYPERPLASIA	1 OF 5		1	4	2	1	2	3	3	
		2 OF 5			1	4	2	2	2	2	
		3 OF 5					1			1	
		4 OF 5								1	
		Total		1	5	6	4	4	5	7	
	INFILTRATE	1 OF 5				1				1	
		2 OF 5				1					
		Total				2				1	
GLAND, SALIVARY, SUBMANDIBULAR		# Animals Examined	11	0	0	10	10	0	3	10	
	INFILTRATE	1 OF 5	1			1	2			1	
		2 OF 5							1	4	
		Total	1			1	2		1	5	

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Organ/ Tissue	Finding	Severity	Group (mg/kg/day)							
			Male				Female			
			0	12	40	120	0	12	40	120
KIDNEY		# Animals Examined	11	0	1	10	10	0	3	10
	CHRONIC PROGRESSIVE NEPHROPATHY	1 OF 5								2
		2 OF 5				2	1			
		Total				2	1			2
	INFILTRATE	1 OF 5	1		1		2			1
		2 OF 5	1			2	2		1	1
		Total	2		1	2	4		1	2
	LYMPHOMA, MALIGNANT								1	
		Total							1	
NERVE, OPTIC		# Animals Examined	11	0	0	10	9	0	3	10
	DEGENERATION/ REGENERATION	2 OF 5				1				
		Total				1				

1= Minimal, 2= Mild, 3= Moderate, 4= Marked, 5= Severe; Source: FDA analysis

In the previously reviewed 28-day repeat-dose toxicology study in dogs (Study Number 00275511, reviewed under IND 142028), ziftomenib was administered twice daily by oral gavage at doses of 20, 60, or 200 mg/kg/day for 28 days. Two unscheduled deaths occurred in high-dose males that were likely due to severe alveolar edema and hemorrhage. Additional histologic findings were noted in the hepatobiliary organs, gastrointestinal (GI) tract, kidney, and lymphoid tissues. It is uncertain if the lung toxicity is directly test article-related or secondary to other drug-mediated effects of the GI tract that resulted in hypovolemic shock. Clinical observations included abnormal feces in all dose groups. Vomitus was observed in animals treated with ≥ 60 mg/kg/day and dehydration was suspected in females treated with 200 mg/kg/day. Toxicity of the GI tract was associated with a dose-dependent decrease in food consumption and an adverse decrease in body weight in animals treated with ≥ 60 mg/kg/day. Gross pathology was observed in the GI tract, hepatobiliary system, and lymphoid tissues, which correlated with microscopic findings of white blood cell infiltration, vacuolation, and lymphoid depletion. Urinalysis demonstrated a dose-dependent increase in urine protein that correlated with microscopic findings of tubular degeneration and membranous glomerulopathy in the kidneys. Increases in liver enzymes were observed. The thymus also had signs of toxicity that included reduced organ size and weight with marked lymphoid depletion. Additionally, there was an increase in the weight of the heart with no microscopic correlates, but an increase in the mean RR interval in high-dose animals that correlated with a decreased heart rate.

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Observations made during the FDA's assessment of the 13-week toxicology study in dogs, some of which were not captured by the Applicant, are included in the tables below. All animals survived to the scheduled euthanization dates. Clinical observations included abnormal feces, reduced activity, hunched posture, wet fur, salivation, and thin appearance. Electrocardiogram readings identified a decrease in heart rate that correlated with increased RR intervals. Notable hematology findings included dose-dependent reversible elevations in basophil, large unstained cell, leukocyte, monocyte, and neutrophil counts. Erythrocyte, hematocrit, and hemoglobin levels were reduced dose-dependently. Alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase, bilirubin, and creatine kinase levels were reversibly elevated. Reversible organ weight increases were observed in the adrenal gland, pituitary gland, thyroid gland, kidney, and liver, while decreases were noted in the prostate, testes, ovaries, uterus, and thymus. Macroscopic findings in the liver, gallbladder, lymph nodes, thymus, and thyroid included reversible discoloring. Microscopic findings were principally noted in the liver and included cholestasis and biliary hyperplasia. Other notable tissues of toxicity included the lymph node, spleen, gall bladder, thymus, ovaries, bone marrow, adrenal glands, parathyroid gland, pituitary gland, and epididymis. A high-dose group female (number 4506) had findings of hyperplasia in several tissues, including the liver, pancreas, thymus, heart, aorta, adrenal glands, and mammary glands.

FDA Table 11. Summary of Body Weight Findings

Study Day	Unit	Group (mg/kg/day)							
		Male				Female			
		0	6	20	60	0	6	20	60
92	kg	8.6	4.08%	9.04%	-9.91%	7.4	8.78%	7.43%	-19.59%
120		9.1			-10.50%	8.0			-15.09%

Test article findings are the percent of control levels

FDA Table 12. Summary of Hematology Findings

Test	Unit	Group (mg/kg/day)							
		Male				Female			
		0	6	20	60	0	6	20	60
Basophils	10 ⁹ /L	0.0	38.46%	223.08%	61.54%	0.0	50.00%	42.11%	89.47%
Eosinophils		0.2	15.57%	68.44%	-27.05%	0.2	128.19%	70.74%	-6.38%
Erythrocytes	10 ¹² /L	6.5	-3.73%	-12.59%	-24.95%	6.9	-7.51%	-13.68%	-30.95%
Hematocrit	%	44	-3.10%	-12.84%	-27.47%	46	-5.79%	-12.36%	-32.96%

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Test	Unit	Group (mg/kg/day)							
		Male				Female			
		0	6	20	60	0	6	20	60
Hemoglobin	g/dL	15	-3.78%	-13.40%	-28.87%	15	-6.23%	-12.46%	-34.86%
Large Unstained Cells	10 ⁹ /L	0.0	29.55%	206.82%	259.09%	0.0	80.00%	110.00%	260.00%
Leukocytes		7.7	27.17%	51.07%	69.60%	8.7	14.53%	28.53%	104.18%
Lymphocytes		2.9	-1.04%	12.76%	-13.37%	2.9	12.59%	9.53%	17.25%
Monocytes		0.5	19.60%	45.51%	107.64%	0.5	-8.81%	30.58%	167.63%
Neutrophils		4.0	48.70%	75.90%	127.18%	5.1	13.63%	36.92%	149.14%
Platelets		253	8.32%	41.88%	-24.95%	293	-8.51%	1.40%	-4.50%
Reticulocytes		32	53.75%	14.61%	9.95%	27	-13.91%	-21.49%	22.71%

Test article findings are the percent of control levels

FDA Table 13. Summary of Clinical Chemistry Findings

Test	Unit	Group (mg/kg/day)							
		Male				Female			
		0	6	20	60	0	6	20	60
Alanine Aminotransferase	U/L	38	-9.07%	9.51%	536.28%	39	-2.12%	-2.75%	633.47%
Albumin	g/dL	3	-1.32%	-5.26%	-26.84%	3	-0.25%	-4.06%	-38.58%
Alkaline Phosphatase	U/L	84	12.06%	-3.66%	1555.73%	76	28.67%	-14.66%	2571.77%
Aspartate Aminotransferase		33	-10.46%	-8.93%	169.39%	30	-8.66%	-12.85%	287.15%
Bilirubin	mg/dL	0.0	-34.00%	-46.00%	152.00%	0.0	50.00%	50.00%	417.65%
Cholesterol		124	3.16%	-20.66%	-21.53%	135	0.99%	-17.95%	-42.82%
Creatine Kinase	U/L	169	4.04%	0.79%	51.43%	142	19.86%	9.99%	130.32%
Creatinine	mg/dL	1	-5.71%	-5.71%	-20.00%	1	1.47%	-7.35%	-26.47%

Test article findings are the percent of control levels

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FDA Table 14. Summary of Organ Weight Findings

Organ/ Tissue	Test	Units	Group (mg/kg/day)							
			Male				Female			
			0	6	20	60	0	6	20	60
GLAND, ADRENAL	Organ to Body Weight Ratio	%	0.013	-10.10%	-1.87%	54.92%	0.014	16.39%	8.24%	85.19%
	Organ to Brain Weight Ratio		1.470	-5.22%	12.04%	40.15%	1.460	27.87%	15.27%	59.04%
	Weight	g	1.1	-5.54%	7.85%	36.95%	1.0	26.49%	13.61%	49.26%
GLAND, PITUITARY	Organ to Body Weight Ratio	%	0.001	20.69%	48.28%	61.64%	0.001	24.62%	35.38%	67.69%
	Organ to Brain Weight Ratio		0.068	26.00%	67.53%	48.97%	0.068	39.89%	44.34%	45.72%
	Weight	g	0.1	25.00%	60.00%	45.00%	0.0	36.84%	42.11%	36.84%
GLAND, PROSTATE	Organ to Body Weight Ratio	%	0.069	-40.24%	31.20%	70.15%				
	Organ to Brain Weight Ratio		7.876	-35.94%	20.13%	71.91%				
	Weight	g	5.8	-36.45%	22.83%	72.42%				
GLAND, THYROID/GLAND, PARATHYROID	Organ to Body Weight Ratio	%	0.007	4.98%	8.33%	54.01%	0.009	-22.33%	8.80%	19.10%
	Organ to Brain Weight Ratio		0.783	10.74%	22.55%	42.74%	0.913	-13.46%	16.50%	2.29%
	Weight	g	0.6	8.19%	17.24%	38.79%	0.6	-15.02%	14.62%	-3.56%
HEART	Organ to Body Weight Ratio	%	0.785	1.20%	1.37%	-0.69%	0.850	-3.79%	-7.16%	-0.76%
	Organ to Brain Weight Ratio		91.148	6.30%	15.31%	-8.55%	91.128	5.37%	0.71%	15.51%
	Weight	g	67.3	5.37%	10.64%	10.74%	63.0	4.20%	-1.27%	20.13%
KIDNEY	Organ to Body Weight Ratio	%	0.487	-0.19%	1.20%	37.80%	0.456	-5.45%	5.92%	28.93%

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Organ/ Tissue	Test	Units	Group (mg/kg/day)							
			Male				Female			
			0	6	20	60	0	6	20	60
	Organ to Brain Weight Ratio		56.47 8	4.72%	15.09%	25.31%	48.973	3.35%	15.75%	9.46%
	Weight	g	41.7	4.16%	10.38%	22.37%	33.8	2.45%	13.38%	3.59%
LIVER/ GALLBLADDER	Organ to Body Weight Ratio	%	2.729	0.05%	3.09%	79.55%	2.716	0.83%	-3.13%	59.54%
	Organ to Brain Weight Ratio	%	315.9 52	5.46%	17.53%	62.78%	291.450	10.01%	5.89%	35.70%
	Weight	g	233.0	4.51%	12.82%	59.15%	201.4	9.02%	3.64%	28.09%
OVARY	Organ to Body Weight Ratio	%					0.011	8.50%	-	32.22%
	Organ to Brain Weight Ratio	%					1.168	21.29%	-	26.49%
	Weight	g					0.8	13.43%	-	30.75%
TESTIS	Organ to Body Weight Ratio	%	0.138	-0.08%	-	25.26%	-	36.05%		
	Organ to Brain Weight Ratio	%	16.00 3	5.54%	-	15.10%	-	41.00%		
	Weight	g	11.8	3.81%	-	18.67%	-	42.56%		
THYMUS	Organ to Body Weight Ratio	%	0.071	-1.03%	49.91%	-	35.64%	0.086	5.77%	63.40%
	Organ to Brain Weight Ratio	%	8.294	3.94%	68.97%	-	35.51%	9.255	16.32%	81.13%
	Weight	g	6.2	1.46%	61.30%	-	37.24%	6.4	15.56%	77.52%
UTERUS/ CERVIX	Organ to Body Weight Ratio	%					0.095	11.19%	-3.25%	-
	Organ to Brain Weight Ratio	%					10.452	22.54%	17.36%	-
	Weight	g					7.7	12.14%	4.50%	-

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FDA Table 15. Summary of Macroscopic Findings

Organ/ Tissue	Finding	Finding Modifier	Severity	Group (mg/kg/day)							
				Male				Female			
				0	6	20	60	0	6	20	60
GALLBLADDER			# Animals Examined	4	4	4	4	4	4	4	4
	Abnormal content	dark; gelatinous;					1				2
		yellow; gelatinous					1				2
	Dilatation					1		2			4
						1		2			4
	Discoloration, pale					1		2			4
					1		2			4	
LIVER			# Animals Examined	4	4	4	4	4	4	4	4
	Discoloration, pale						4				4
								4			4
	Focus, pale	multifocal; white									1
											1
	Irregular surface	roughened									1
										1	
LYMPH NODE, MESENTERIC			# Animals Examined	4	4	4	4	4	4	4	4
	Discoloration, dark	green; mottled					1				2
								1			2
	Discoloration, mottled							1			1
								1			1
	Enlargement							2			3
							2			3	
DUCT, BILE			# Animals Examined	0	0	0	1	0	0	0	2
	Dilatation						1				2
								1			2
GLAND, THYROID			# Animals Examined	4	4	4	4	4	4	4	4
	Discoloration, pale	bilateral					1				2
								1			2
THYMUS			# Animals Examined	4	4	4	4	4	4	4	4
	Small						2				1
								2			1

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Organ/ Tissue	Finding	Finding Modifier	Severity	Group (mg/kg/day)							
				Male				Female			
				0	6	20	60	0	6	20	60
CERVIX			# Animals Examined	0	0	0	0	4	4	4	4
	Enlargement									1	1
				Total							1
LUNG			# Animals Examined	4	4	4	4	4	4	4	4
	Discoloration, pale	right, middle lobe					1				
				Total				1			
PANCREAS			# Animals Examined	4	4	4	4	4	4	4	4
	Discoloration, pale						1				
				Total				1			
VAGINA			# Animals Examined	0	0	0	0	4	4	4	4
	Enlargement									1	1
				Total							1

FDA Table 16. Summary of Microscopic Findings

Organ/ Tissue	Finding	Finding Modifier	Severity	Group (mg/kg/day)							
				Male				Female			
				0	6	2	60	0	6	20	60
LIVER			# Animals Examined	4	4	4	4	4	4	4	4
	ACCUMULATION	basophilic; bile duct	1 OF 5			3	1				1
			2 OF 5				3				3
			Total			3	4				4
	CELLULARITY, INCREASED	basophilic; macrophage	2 OF 5				2				3
			3 OF 5								1
			Total				2				4
	CHOLESTASIS		1 OF 5			1					
			2 OF 5				2				2
			3 OF 5				2				2
			Total			1	4				4
	HYPERPLASIA	biliary	1 OF 5			2					
			2 OF 5			1					1
			3 OF 5				1				2
			4 OF 5				3				1

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Komzifti (ziftomenib)

Organ/ Tissue	Finding	Finding Modifier	Severity	Group (mg/kg/day)									
				Male				Female					
				0	6	2	60	0	6	20	60		
			Total			3	4						4
	INFILTRATE	mononuclear cell; ductular	1 OF 5									1	
			Total									1	
	INFLAMMATION	mixed cell; periportal	1 OF 5			2	2						2
			2 OF 5				2						2
			Total			2	4						4
	PIGMENT	macrophage	1 OF 5			2							
			2 OF 5				2						3
			3 OF 5										1
			Total			2	2						4
	VACUOLATION	hepatocellular	3 OF 5				3						3
			4 OF 5				1						1
			Total				4						4
			# Animals Examined	4	4	4	4	4	4	4	4	4	4
	CELLULARITY, DECREASED	lymphocyte	1 OF 5			2	4					1	1
			2 OF 5										3
			Total			2	4					1	4
	CELLULARITY, INCREASED	pigmented macrophage; vacuolated macrophage	1 OF 5				2	2	1	4	1		1
			2 OF 5				3			1	3		3
		vacuolated macrophage	3 OF 5										1
			Total				4	2	1	4	4		4
	CONGESTION		1 OF 5			2	1		3	1			
			2 OF 5		1	1	2	2	1	3	2		2
			3 OF 5				1						2
			Total		1	3	4	2	4	4	4		4
			# Animals Examined	4	4	4	4	4	4	4	4	4	4
	CELLULARITY, DECREASED	lymphocyte	1 OF 5			1	2						4
			2 OF 5				1						
			Total			1	3						4
	CELLULARITY, INCREASED	histiocytic cell; vacuolated macrophage	1 OF 5				4						
			2 OF 5				3						4

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Komzifti (ziftomenib)

Organ/ Tissue	Finding	Finding Modifier	Severity	Group (mg/kg/day)									
				Male				Female					
				0	6	2	60	0	6	20	60		
			Total				4					4	
	SIDEROTIC PLAQUE		1 OF 5				1		1			1	
			Total				1		1			1	
	EPIDIDYMIS			# Animals Examined	4	4	4	4	0	0	0	0	0
IMMATURITY							4						
			Total				4						
SPERM GRANULOMA			2 OF 5	1									
			Total	1									
SPERM, DECREASED		luminal		1 OF 5			3						
				2 OF 5			1						
				4 OF 5				4					
			Total			4	4						
GALLBLADDER			# Animals Examined	4	4	4	4	4	4	4	4	4	
	ACCUMULATION	basophilic		1 OF 5			1					3	
				2 OF 5			3					1	
				Total			4					4	
	CELLULARITY, INCREASED	basophilic; macrophage		1 OF 5			1					3	
				2 OF 5			3					1	
				Total			4					4	
	HYPERPLASIA		2 OF 5		1								
		Total		1									
LYMPH NODE, MANDIBULAR			# Animals Examined	4	4	4	4	4	4	4	4	4	
	CELLULARITY, DECREASED	lymphocyte		1 OF 5			4			1	2		
				Total			4			1	2		
	CELLULARITY, INCREASED	pigmented macrophage; vacuolated macrophage		1 OF 5			4	1	1	1	4		
				Total			4	1	1	1	4		
	CONGESTION		2 OF 5		1						1		
		Total		1						1			
GUT-ASSOCIATED			# Animals Examined	4	4	4	4	4	4	4	4	4	
	CELLULARITY, DECREASED	lymphocyte	1 OF 5				1				3		

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Organ/ Tissue	Finding	Finding Modifier	Severity	Group (mg/kg/day)										
				Male				Female						
				0	6	2	60	0	6	20	60			
LYMPHOID TISSUE			2 OF 5				3							
			Total				4						3	
	CELLULARITY, INCREASED	vacuolated macrophage	1 OF 5			3								1
			2 OF 5				3							3
			Total			3	3							4
THYMUS			# Animals Examined	4	4	4	4	4	4	4	4	4	4	
	CELLULARITY, DECREASED	lymphocyte	2 OF 5				1							1
			3 OF 5				1							2
			4 OF 5				1							1
			Total				3							4
	CYST							1						1
		Total						1						1
	HEMORRHAGE	interstitial	2 OF 5		1									
			Total		1									
	HYPERPLASIA	adipose tissue	2 OF 5											1
			Total											1
BONE MARROW, STERNUM			# Animals Examined	4	4	4	4	4	4	4	4	4	4	
	CELLULARITY, DECREASED	hematopoietic cells	1 OF 5				1							2
			2 OF 5				1							1
			Total				2							3
	HEMORRHAGE		2 OF 5				1							
		Total					1							
	NECROSIS		2 OF 5											1
Total													1	
TESTIS			# Animals Examined	4	4	4	4	0	0	0	0	0	0	
	INDETERMINATE	sexual maturity				4								
			Total			4								
	PERIPUBERTAL			4	4									
		Total		4	4									
	VACUOLATION	seminiferous tubule	2 OF 5				4							
Total						4								

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Komzifti (ziftomenib)

Organ/ Tissue	Finding	Finding Modifier	Severity	Group (mg/kg/day)							
				Male				Female			
				0	6	2	60	0	6	20	60
DUCT, BILE			# Animals Examined	0	0	0	1	0	0	0	2
	ACCUMULATION	basophilic	1 OF 5				1				1
			Total				1				1
	CELLULARITY, INCREASED	basophilic; macrophage	1 OF 5								2
			2 OF 5				1				
Total						1				2	
GLAND, ADRENAL			# Animals Examined	4	4	4	4	4	4	4	4
	CYST							1			
			Total					1			
	HYPERTROPHY/ HYPERPLASIA	cortical	1 OF 5				2				3
			2 OF 5				1				
			Total				3				3
	VACUOLATION	cortical	1 OF 5	1		1					
Total			1		1						
GLAND, PARATHYROID			# Animals Examined	3	4	4	3	3	3	3	4
	CYST					1					3
			Total			1					3
GLAND, PITUITARY			# Animals Examined	4	4	4	4	4	4	4	4
	CYST			2	1	3	1	1	2	1	1
			Total	2	1	3	1	1	2	1	1
GLAND, PROSTATE			# Animals Examined	4	4	4	4	0	0	0	0
	IMMATURITY						3				
			Total				3				
LUNG			# Animals Examined	4	4	4	4	4	4	4	4
	HEMORRHAGE	alveolus/duct	1 OF 5		1						
			Total		1						
	INFILTRATE	histiocytic; mixed cell; mixed cell, FOCAL	1 OF 5		1		2			1	1
			Total		1		2			1	1
INFLAMMATION	mixed cell, FOCAL	2 OF 5		1							

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Komzifti (ziftomenib)

Organ/ Tissue	Finding	Finding Modifier	Severity	Group (mg/kg/day)									
				Male				Female					
				0	6	2	60	0	6	20	60		
			Total		1								
SKIN			# Animals Examined	4	4	4	4	4	4	4	4	4	4
	INFILTRATE	mixed cell; perifollicular, FOCAL; mononuclear cell; follicle; mononuclear cell; follicle, FOCAL	1 OF 5		1	1	1			1			
		Total			1	1	1			1			
	INFLAMMATION	mixed cell; glandular	2 OF 5			1							
		Total				1							
	PARASITE	follicle, FOCAL	1 OF 5		1		1		1				
Total				1		1		1					
ARTERY, AORTA			# Animals Examined	4	4	4	4	4	4	4	4	4	
	HYPERPLASIA	adipose tissue	2 OF 5									1	
		Total										1	
BRAIN			# Animals Examined	4	4	4	4	4	4	4	4	4	
	VACUOLATION	medulla oblongata	2 OF 5									1	
		Total										1	
CERVIX			# Animals Examined	0	0	0	0	4	4	4	4	4	
	EDEMA		1 OF 5									1	
		Total										1	
GLAND, MAMMARY			# Animals Examined	4	4	4	4	4	4	4	4	4	
	HYPERPLASIA	adipose tissue	2 OF 5									1	
		Total										1	
HEART			# Animals Examined	4	4	4	4	4	4	4	4	4	
	HEMORRHAGE	endocardial	1 OF 5								1		
		Total									1		
	HYPERPLASIA	adipose tissue	2 OF 5									1	
		Total										1	
	MINERALIZATION	vascular, FOCAL	2 OF 5			1							
Total					1								

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Komzifti (ziftomenib)

Organ/ Tissue	Finding	Finding Modifier	Severity	Group (mg/kg/day)								
				Male				Female				
				0	6	2	60	0	6	20	60	
PANCREAS			# Animals Examined	4	4	4	4	4	4	4	4	4
	HYPERPLASIA	adipose tissue	2 OF 5									1
		Total										1
	INFILTRATE	mononuclear cell; ductular; mononuclear cell; vascular/perivascular	1 OF 5		1				1			
Total			1				1					
TRACHEA			# Animals Examined	4	4	4	4	4	4	4	4	4
	INFLAMMATION	mixed cell	1 OF 5									1
			3 OF 5				1					
		Total				1						1
VAGINA			# Animals Examined	0	0	0	0	4	4	4	4	4
	EDEMA		2 OF 5									1
		Total										1
OVARY			# Animals Examined					4	4	4	4	4
	CORPORA LUTEA, INCREASED NUMBER		1 OF 5						1			
	CORPORA LUTEA, INCREASED NUMBER		Total						1			
	IMMATURITY	Follicle						2	4	4	4	4
	IMMATURITY		Total					2	4	4	4	4

1 = Minimal, 2 = Mild, 3 = Moderate, 4 = Marked, 5 = Severe; Source: FDA analysis

5.5.2. Genetic Toxicology

The Applicant’s Position:

Ziftomenib was not genotoxic in the GLP-compliant standard genotoxicity testing battery conducted to support registration. Ziftomenib was demonstrated to be nonmutagenic in a bacterial reverse mutation assay and nonclastogenic/aneugenic in an in vitro micronucleus assay conducted in human peripheral blood lymphocytes and in an in vivo micronucleus assay conducted in CD-1 mice.

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Komzifti (ziftomenib)

KO-539 Bacterial Reverse Mutation Assay / KO-TOX-0014 / Section 4.1 of Module 2.6.6 and Section 8 Module 2.6.7.	
Key findings:	
Under the conditions of this study, ziftomenib was determined to be negative (nonmutagenic) in the bacterial reverse mutation assay.	
Study Type	In Vitro Reverse Mutation Assay in Bacterial Cells
GLP Compliance	Yes
Test System	Plate incorporation method using <i>S. typhimurium</i> tester strains TA98, TA100, TA1535, and TA1537 and <i>E. coli</i> tester strain WP2uv rA in the presence and absence of metabolic activation (Aroclor™ 1254-induced rat liver S9 microsomal fraction). In the range-finding assay, ziftomenib was tested in single plates at 1.0, 5.0, 10, 50, 100, 500, 1000, and 5000 µg/plate with strains TA100 and WP2 uvrA. In the mutagenicity assay, ziftomenib was tested at 12.5, 25, 50, 100, 250, 500, 1000, and 2500 µg/plate. Criteria for a negative response were met for all tester strains with and without metabolic activation. The data from the vehicle and positive controls demonstrated the validity and sensitivity of this test system for detecting chemical mutagens with and without metabolic activation.

KO-539 In Vitro Micronucleus Assay in Cultured Human Peripheral Blood Lymphocytes / KO-TOX-0015 / Section 4.2 of Module 2.6.6 and Section 8 Module 2.6.7.	
Key findings:	
Under the conditions of this study, ziftomenib was considered negative (nonclastogenic/aneugenic) when evaluated in the in vitro micronucleus assay conducted in HPBLs.	
Study Type	In Vitro Micronucleus Assay
GLP Compliance	Yes
Test System	Ziftomenib was evaluated for the potential to induce micronuclei in HPBLs during short (4-hour) and long (24-hour) incubations with or without an exogenous metabolic activation system (Aroclor 1254-induced rat liver S9 microsomal fraction) in cultured human peripheral blood lymphocytes (HPBL). The concentrations selected for micronucleus evaluation in all treatments were based on cytotoxicity. Micronuclei were evaluated in 2000 binucleated cells per concentration.

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	The results from the vehicle and positive controls demonstrated the validity and sensitivity of the test system for detecting chemical clastogens and aneugens in the presence and absence of metabolic activation.

An In Vivo Micronucleus Assay of KO-539 by Oral Gavage in CD-1 Mice / KO-TOX-0016 / Section 4.3 of Module 2.6.6 and Section 9 Module 2.6.7.

Key findings:

- Ziftomenib did not produce any increases (vs control) in the mean number of micronucleated polychromatic erythrocytes in CD-1 mice. No bone marrow cytotoxicity (ie, decreases in the ratio of polychromatic to total erythrocytes) was noted for either sex at any dose level evaluated. Under the conditions of this study, ziftomenib met the criteria for a negative response for bone marrow cytotoxicity and clastogenicity/aneugenicity.

Study Type	In vivo bone marrow micronucleus test in CD-1 mice
GLP Compliance	Yes
Test System	Ziftomenib was formulated in vehicle (20% w/v Captisol in RO DI water with 3.0 molar equivalent (b) (4) pH (b) (4) and administered to CD-1 mice via oral gavage at doses of 0 mg/kg bid (0 mg/kg/day), 150 mg/kg bid (300 mg/kg/day), 300 mg/kg bid (600 mg/kg/day), and 600 mg/kg bid (1200 mg/kg/day) on 2 consecutive days of treatment. Daily doses were administered at least 6 hours, but not more than 7 hours, apart. Vehicle and positive control (cyclophosphamide) groups were included in the study design. Due to test article related deaths at 600 (n=2 male animals) and 1200 mg/kg/day (n=5 male animals) an additional vehicle and low dose treatment group (75 mg/kg bid or 150 mg/kg/day; n=5 male animals each) were added.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment of genotoxicity.

5.5.3. Carcinogenicity

The Applicant's Position:

No carcinogenicity studies have been conducted with ziftomenib.

The FDA's Assessment:

The FDA concurs. Carcinogenicity studies were not warranted for the proposed indication.

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5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Reproductive and developmental toxicity studies conducted with ziftomenib are limited to dose-range finding and definitive embryo-fetal studies in mice. As the definitive study was positive for teratogenicity, a confirmatory study in a second species (eg, rabbit) was not warranted.

Per the ICH S9 guideline, studies of fertility and early embryonic development or pre- and postnatal toxicology are not warranted and therefore were not performed. In the 13-week repeat dose toxicity study in dogs test article-related microscopic findings in the reproductive tracts were observed after dosing at 6, 20, or 60 mg/kg/day indicating a potential adverse effect of ziftomenib on human fertility. Juvenile animal studies were not conducted, consistent with the guidance provided in the ICH S9 guideline.

An Oral (Gavage) Dose Range-Finding Study of the Effects of KO-539 on Embryo/Fetal Development in Mice / KO-TOX-0017 / Section 6.1 of Module 2.6.6 and Section 11 Module 2.6.7.	
Key Findings:	
Based on findings in the high dose group (200 mg/kg/day) including significantly increased postimplantation loss (+94.6% vs control) and external malformations such as cleft palate ziftomenib dosages of 6, 20, and 60 mg/kg/day (3, 10, and 30 mg/kg bid, respectively) were selected for evaluation in the definitive EFD study in mice.	
GLP compliance: No	
Methods	
Dose and frequency of dosing:	0 (vehicle) mg/kg bid (0 mg/kg/day), 10 mg/kg bid (20 mg/kg/day), 30 mg/kg bid (60 mg/kg/day), and 100 mg/kg bid (200 mg/kg/day) during GDs 6 through 15. Daily doses were administered at least 6 hours, but not more than 7 hours, apart.
Route of administration:	Oral Gavage
Formulation/Vehicle:	(b) (4) in RO DI water with 3.0 molar equivalent (b) (4) pH (b) (4)
Species/Strain:	Mouse, CD-1
Number/Sex/Group:	n=8 pregnant female animals/group
Age:	12 weeks
Satellite groups:	No

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Study design:	Assessment of embryofetal development Day of Mating: GD 0; animals were dose during GDs 6 through 15. Day of Laparohysterectomy: GD 18
Major Findings	All dams survived to scheduled necropsy on GD 18. No remarkable clinical observations were noted at any dose level during the dosing or postdosing phases. At 200 mg/kg/day: In dams mean body weight was significantly decreased (-17.5% vs control) on GD 16. In addition, mean gravid uterine weight was significantly decreased (-90.8% vs control). These effects were considered secondary to the entirely resorbed litters noted for 6 of 7 dams at 200 mg/kg/day. Mean litter proportion of postimplantation loss was significantly increased (+94.6% vs control) at 200 mg/kg/day, with a corresponding lower mean number of live fetuses (0.4 per dam). Six of seven gravid females in this group had entirely resorbed litters (primarily early resorption), thus precluding evaluation of fetal weight at this dose level. At 60 mg/kg/day, decreased (-8.9% to -11.1% vs control) mean fetal body weight values (males, females, and combined sex) were noted. Intrauterine survival at 20 and 60 mg/kg/day and intrauterine growth at 20 mg/kg/day were unaffected by ziftomenib administration. External malformations were limited to cleft palate (entire length) for 1 (1), 4 (2), and 1 (1) fetuses (litters) at 20, 60, and 200 mg/kg/day, respectively.

An Oral (Gavage) Study of the Effects of KO-539 on Embryo-Fetal Development in Mice / KO-TOX-0018 / Section 6.2 of Module 2.6.6 and Section 13.1 Module 2.6.7.

Key Findings:

- Ziftomenib was well tolerated maternally. The maternal NOAEL was established at the high dose level (60 mg/kg/day).
- Adverse effects on intrauterine growth and survival, as well as fetal external and skeletal malformations, were noted at 60 mg/kg/day, resulting in a developmental NOAEL of 20 mg/kg/day.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 mg/kg bid (0 mg/kg/day), 3 mg/kg bid (6 mg/kg/day), 10 mg/kg bid (20 mg/kg/day), and 30 mg/kg bid (60 mg/kg/day) during GDs 6 through 15. Daily doses were administered at least 6 hours, but not more than 7 hours, apart.

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Route of administration:	Oral Gavage
Formulation/Vehicle:	(b) (4) in RO DI water with 3.0 molar equivalent (b) (4) pH (b) (4)
Species/Strain:	Mouse, CD-1
Number/Sex/Group:	n=25 pregnant female animals/group
Age:	approximately 12 weeks
Satellite groups:	Toxicokinetics of ziftomenib and its metabolites KO-516, and KO-739; vehicle n=6 treatment groups n=48
Study design:	Assessment of embryofetal development Day of Mating: GD 0; animals were dose during GDs 6 through 15. Day of Laparohysterectomy: GD 18
Parameters	Major Findings
Mortality	All dams survived to scheduled necropsy on GD 18.
Clinical Signs	There were no ziftomenib-related clinical observations noted at any dose level during the dosing or postdosing phases.
Body weights	Mean maternal body weight was unaffected at all dose levels evaluated.
Reproductive and developmental findings	<u>At 60 mg/kg/day:</u> decreased mean fetal body weight values (-11.1% to -12.3% vs control), higher number of dead fetuses (0.9 fetuses/litter) compared to the control group (0.0 fetuses/litter), fetal external malformation of cleft palate (32 fetuses in 11 litters, confirmed skeletally as split palatine in the skull [14 fetuses in 6 litters]) and skeletal malformations of fused cervical arches (33 fetuses in 12 litters) and absent lumbar vertebrae (12 fetuses in 3 litters). Significantly increased (vs control) mean litter proportions of skeletal developmental variations (fused and/or misaligned costal cartilage, short rib, supernumerary site in the suture bone, and/or fused, unossified, and/or incompletely ossified sternebrae) were considered secondary to the decreased fetal body weight values noted at 60 mg/kg/day. The maternal NOAEL for ziftomenib was established at 60 mg/kg/day. Based on decreased mean fetal body weight values and adverse fetal external and skeletal malformations noted at 60 mg/kg/day, the NOAEL for developmental toxicity was considered to be 20 mg/kg/day.
Toxicokinetics	Systemic exposure (C_{max} and AUC _{0-24h}) to ziftomenib, KO-516, and KO-739 increased with increasing ziftomenib dose in a generally dose-proportional manner across the dose range on GDs 6 and 15. There was no evidence of meaningful accumulation of any analyte in plasma

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on GD 15 relative to GD 6. Systemic exposure (AUC_{0-24h}) to the 2 metabolites (KO-516 and KO-739) was less than that to the parent molecule (ziftomenib) on GDs 6 and 15. Maternal systemic exposure (AUC_{0-24h}) to ziftomenib at the developmental NOAEL on GD 15 was 14,500 ng*h/mL. Corresponding values for the KO-516 and KO-739 metabolites were 3820 ng*h/mL and 2190 ng*h/mL, respectively.

Analyte	Dose (mg/kg/day)	C _{max} (ng/mL)		AUC _{0-24h} (ng*hr/mL)	
		GD 6	GD 15	GD 6	GD 15
Ziftomenib	6	260	237	2610	3430
	20	979	996	12,000	14,500
	60	2640	2190	35,000	34,900
KO-516	6	49.1	47.6	572	652
	20	245	222	3290	3820
	60	724	588	11,100	11,200
KO-739	6	29.1	30.0	NA ^a	433
	20	130	147	1900	2190
	60	332	314	5670	5920

Abbreviations: AUC=area under the plasma concentration-time curve; AUC_{0-24h}=area under the plasma concentration-time curve from time 0 to 24 hours; C_{max}=maximum plasma concentration; GD=Gestation Day; NA=not applicable.

^a AUC_{0-24h} not reported due to %AUC_{extra} >25%.

The FDA's Assessment:

The FDA agrees with the Applicant that fertility and early embryonic developmental studies were not warranted for the proposed indication. The FDA agrees with the Applicant's assessment of the embryo-fetal toxicity. The following assessment provides additional information to support the statements regarding the data in the label.

In the embryo-fetal development study, pregnant mice received ziftomenib doses of 6, 20, or 60 mg/kg/day on gestation days 6-15, and the dosing period was followed by a period of no dosing on gestation days 16-18. Maternal body weight and weight gains were lower in the high-dose animals by the end of the dosing period and continued to the end of the recovery period. There were no macroscopic findings compared to controls throughout the study. Post-implantation loss was higher in the high-dose group and is due to the higher number of dead fetuses, which in turn was mainly due to 1 high-dose group animal that had a litter entirely composed of dead fetuses

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(16 fetuses, 100% post-implant loss). Mean fetal weights were modestly lower in all test article groups. External malformations were notably elevated in the high-dose group fetuses and were almost entirely cleft palates. There were few visceral malformations. Skeletal malformations were observed most frequently and were almost entirely in the high-dose group. These were observed in the ribs (absent), skull (split palatine), and vertebra (fused cervical arches and absent lumbar and thoracic vertebra). The AUCs at 6, 20, and 60 mg/kg on GD15 were 3430, 14,500, and 34,900 hr*ng/mL, respectively, and the clinical AUC at the recommended dose of 600 mg once daily was 13,185 hr*ng/mL, resulting in exposure multiples of 0.3 to 2.65 (approximately 3).

FDA Table 17. Summary of Maternal Body Weight Findings (% of Control Weight (Grams))

mg/kg/day	0			6		20		60	
Body weight (GD 15)	48.4	47.1	-2.77	48.4	0.08	47.2	-2.46		
Body weight (GD 18)	58.7	56.0	-4.49	58.8	0.18	54.8	-6.67		
Body weight gain (GD 13-15)	6.4	5.7	-11.0	6.4	-1.24	5.5	-13.69		
Body weight gain (GD 16-18)	7.2	6.1	-15.14	6.6	-7.92	5.8	-19.03		
Gravid uterus weight	23.0	22.6	-1.90	23.7	2.87	21.0	-8.64		
Adjusted body weight	35.0	33.5	-4.4	34.9	-0.5	33.9	-3.4		
Adjusted body weight gain	6.4	4.9	-25.7	6.1	-8.6	5.5	-17.5		

Where indicated, test article findings are the percent of control levels

FDA Table 18. Summary of Cesarean Section Findings (% of Control Weight (Grams))

mg/kg/day	0			6		20		60	
Number of pregnant females	22	21	-4.55	22	0	22	0		
Female with live fetuses	22	21	-4.55	22	0	21	-4.55		
Female with resorptions	12	11	4.8	8	-47.6	9	-23.8		
Early resorptions	0.8	0.8	4.8	0.3	-64.7	0.5	-35.3		
Late Resorptions	0.2	0.2	4.8	0.2	25.0	0.2	25.0		
Number of fetuses	13.6	14.0	3.0	14.6	7.3	14.0	3.0		
Number of live fetuses	13.6	14.0	3.0	14.6	7.3	13.3	-2.3		
Number of dead fetuses	0.0	0.0	0	0.0	0	0.9	-		
Post-implantation loss	6.9	6.6	-4.37	3.2	-53.66	10.6	54.88		

Where indicated, test article findings are the percent of control levels

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FDA Table 19. Summary of Fetal Findings

mg/kg/day	0	6	20	60
Mean fetal weight (% change vs. control)	-	-7.51	-5.94	-11.88
External malformations (fetuses/litters)				
Total evaluated	300/22	297/21	324/22	311/22
Malformations	1/1	4/2	1/1	32/11
Cleft palate	1/1	4/2	0/0	32/11
Visceral malformations (fetuses/litters)				
Total evaluated	300/22	297/21	324/22	311/22
All malformations	0/0	0/0	1/1	0/0
Small kidney	0/0	0/0	1/1	0/0
Skeletal malformations (fetuses/litters)				
Total evaluated	300/22	297/21	324/22	311/22
All malformations	0/0	1/1	0/0	52/15
Rib (absent)	0/0	0/0	0/0	2/2
Skull (split palatine)	0/0	1/1	0/0	14/6
Vertebra (fused cervical arch, absent lumbar, absent thoracic)	0/0	0/0	0/0	46/15

In the dose range-finding embryo-fetal development study in mice, pregnant females received twice-daily ziftomenib doses of 20, 60, or 200 mg/kg/day on gestation days 6-15, and the dosing period was followed by a period of no dosing on gestation days 16-18. Lower maternal body weights were seen at the high dose by the end of the dosing period compared to controls. The high dose group only had a single female with live fetuses compared to 7 or 8 in the other groups. External malformations included open eye and cleft palate. These were observed in all the test article groups. Based on the results, dose levels of 6, 20, and 60 mg/kg/day were selected for a definitive embryo-fetal development study.

5.5.5. Other Toxicology Studies

The Applicant's Position:

Phototoxicity

In a 3T3 neutral red uptake (NRU) phototoxicity assay, ziftomenib demonstrated phototoxic potential. However, in an in vivo phototoxicity study conducted in hairless mice, no evidence of cutaneous phototoxicity was noted indicating that ziftomenib does not present a phototoxic hazard to humans.

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Neutral Red Uptake Phototoxicity Assay of KO-539 in BALB/c 3T3 Mouse Fibroblasts / KO-TOX-0019 / Section 8.1 of Module 2.6.6 and Section 17 Module 2.6.7.	
Key Findings: ziftomenib was demonstrated to have phototoxic potential	
Study Type	In vitro photosafety testing with BALB/c 3T3 mouse fibroblasts
GLP compliance	Yes
Test System	The phototoxicity potential of ziftomenib was measured by the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to ziftomenib and ultraviolet radiation (UVR) as compared to the viability of fibroblasts exposed to ziftomenib in the absence of UVR. OECD 432-recommended cell survival and OD540 criteria and promethazine cytotoxicity and phototoxicity criteria were met indicating that the assays were valid.

Ziftomenib: Oral (Gavage) Phototoxicity Evaluation in Hairless Mice / KO-TOX-0020 / Section 8.2 of Module 2.6.6 and Section 17 Module 2.6.7.	
Key Findings: There was no evidence of cutaneous phototoxicity as evidenced by dermal scoring.	
GLP compliance: Yes	
Methods	
Dose and frequency of dosing:	0 mg/kg bid (0 mg/kg/day), 20 mg/kg bid (40 mg/kg/day), 60 mg/kg bid (120 mg/kg/day), 200 mg/kg bid (400 mg/kg/day). Daily doses were administered at least 6 hours, but not more than 7 hours, apart for 3 consecutive days.
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) in RO DI water with 3.0 molar equivalent (b) (4) pH (b) (4)
Species/Strain:	Hairless mice (CrI:SKH1- <i>hr</i>), females
Number/Sex/Group:	Vehicle: n= 5 female animals treatment groups: n=10 feamles/group
UVR exposure (UVB, UVA, visible light from a xenon lamp)	approximately 4 hours after the final dose administration
Results	There was no evidence of cutaneous phototoxicity as evidenced by dermal scoring.

The FDA's Assessment:

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The FDA agrees with the Applicant’s assessment.

Impurity specifications assessment

Acceptance criteria for impurities in the ziftomenib drug substance with proposed limits over the ICH Q3A qualification threshold of 0.15% were qualified by the levels in the GLP repeat-dose toxicology studies in dogs. FDA Table 20 summarizing the findings is below.

FDA Table 20. Qualification of Selected Impurities

			13-week dog tox study			
Impurity	Proposed limit	Level in 600 mg/day (clinical administration)	Level in tox batch (%) (Batch number PS06580-45-E-P)	Impurity level at 13-week dog tox HNSTD (b) (4)	Safety margin	Qualified? (b) (4)
			28-day dog tox study			
			Level in tox batch (%) (Batch number PS02684-20-E-P1)	Impurity level at 28-day dog tox HNSTD (b) (4)	Safety margin (b) (4)	Qualified? Yes

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Ziftomenib is an orally administered small molecule that inhibits the interaction between menin and histone-lysine N-methyltransferase 2A enzyme (KMT2A) fusion proteins. The Applicant is seeking approval of ziftomenib for the treatment of adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with a nucleophosmin 1 (*NPM1*) mutation (*NPM1-m*). The proposed ziftomenib dosage is 600 mg daily (QD).

The clinical pharmacology section of the NDA is supported by the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy data from the registrational Phase 1/2 study KO-MEN-001 and the clinical pharmacology studies KO-MEN-003 (food effect and drug-drug interaction [DDI] study with gastric acid-reducing agent [ARA]) and KO-MEN-005 (mass-balance and absolute bioavailability [BA]).

The clinical pharmacology review focused on the assessment of the acceptability of the proposed ziftomenib dosage and dosing guidance with regard to (1) food, (2) concurrent use with cytochrome P450 (CYP) 3A inhibitors and inducers, (3) coadministration with ARAs, and (4) renal and hepatic impairment (RI and HI, respectively).

Specific recommendations/comments are summarized in FDA Table 21.

FDA Table 21. Clinical Pharmacology Review Issues, Recommendations, and Comments

Review Issues	Recommendations and Comments
Evidence of effectiveness	The primary evidence of effectiveness comes from the Phase 1/2 pivotal study KO-MEN-001 [Section 6.3.2.1]. In the <i>NPM1-m/KMT2A</i>-rearrangement dose expansion phase, ziftomenib demonstrated better activity at 600 mg versus 200 mg (complete response [CR]/complete hematologic response [CRh] 25% vs 0%). In the <i>NPM1-m</i> modified intention-to-treat (mITT) dataset, CR + CRh was 21% (n=112, Phase 1b efficacy analysis set [EAS] + Phase 2).
General dosing instructions	The recommended dosage is 600 mg QD to be administered on an empty stomach (at least 1 hour before or 2 hours after a meal) [Section 6.3.2.2, 6.3.2.4]. Administration with a high-fat meal increases exposure ~4-fold compared to fasted administration.

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Dosing in patient subgroups	Intrinsic factors [Section 6.3.2.3] <u>Organ impairment:</u> No dosage adjustments are recommended in mild-to-moderate RI or HI. There is no clinically significant effect of mild-to-moderate RI (creatinine clearance [CL_{Cr}] 30 to 89 mL/min) or HI (bilirubin less than or equal to upper limit of normal [ULN] and aspartate aminotransferase [AST] greater than ULN or bilirubin less than or equal to 3 x ULN) on ziftomenib PK. The impact of severe RI or HI is unknown. Post-marketing requirements (PMRs) will be issued to evaluate the impact of severe RI and HI on ziftomenib PK. <u>Other intrinsic factors:</u> No dosage adjustments are recommended based on age, sex, race, ethnicity, body weight or body surface area (BSA). There is no clinically significant effect of age (18 to 86 years), sex (51% female), race (75% White, 5.3% Black or African American, 3.2% Asian), ethnicity (6.3% Hispanic or Latino), body weight (41 to 135 kg), or BSA (1.40 to 2.46 m²) on ziftomenib PK. Extrinsic factors [Section 6.3.2.4] Metabolic DDIs <u>Strong or moderate CYP3A inhibitors:</u> No dosage adjustments are recommended in patients receiving strong or moderate CYP3A inhibitors; however, additional safety monitoring is recommended. Ziftomenib is primarily metabolized by CYP3A. Concomitant use of strong CYP3A inhibitors increases ziftomenib exposure by ~2-fold, which may increase risk of adverse reactions such as QTc prolongation. The Applicant has an ongoing study, Study KO-MEN-001 Sub-study 2, to evaluate the impact of itraconazole (strong CYP3A and P-gp inhibitor) on ziftomenib PK. Given that the study is ongoing, a PMR will be issued for its completion. <u>Strong or moderate CYP3A inducers:</u> Concomitant use of strong or moderate CYP3A inducers should be avoided. Ziftomenib is primarily metabolized by CYP3A. Concomitant use of strong or moderate CYP3A inducers may decrease ziftomenib exposure, which may decrease efficacy.

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	<u>CYP3A substrates:</u> No dosage adjustments are recommended for concurrent use of CYP3A substrates. The Applicant has an ongoing study, Study KO-MEN-001 Sub-study 1, to evaluate the impact of ziftomenib (<i>in vitro</i> CYP3A inhibitor) on midazolam PK. Given that the study is ongoing, a PMR will be issued for its completion. <i>Transporter DDIs</i> <u>P-glycoprotein (P-gp) inhibitors:</u> No dosage adjustments are recommended for concomitant use of P-gp inhibitors. <u>Breast cancer resistance protein (BCRP) inhibitors:</u> The impact of concomitant use of BCRP inhibitors on ziftomenib PK is unknown. A PMR will be issued to evaluate the impact of BCRP inhibitors on ziftomenib PK. <i>ARA DDIs</i> <u>Proton pump inhibitors (PPIs):</u> Concomitant use of PPIs should be avoided. Concomitant use of PPIs decreases ziftomenib exposure by ~60 to 70%, which may decrease efficacy. <u>Histamine-2 receptor antagonists (H2RAs):</u> Administration of H2RAs should be staggered 10 hours before or 2 hours after KOMZIFTI administration. <u>Antacids:</u> Administration of antacids should be staggered 2 hours before or 2 hours after KOMZIFTI administration. <i>Other DDIs</i> <u>QTc-prolonging drugs:</u> Concomitant use of QTc-prolonging drugs should be avoided. If concurrent use cannot be avoided, additional safety monitoring is recommended. Interrupt administration if QTc interval is > 500 ms or change from baseline is > 60 ms. Patients receiving ziftomenib 600 mg displayed a concentration-dependent increase in QTc interval (largest mean increase in QTc predicted to be 7.7 ms), with 8% of patients experiencing QTcF > 500 ms and QTc increase > 60 ms over baseline.
Labeling	The following dosage modifications and management strategies are recommended in the labeling:

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	<u>Strong or moderate CYP3A inhibitors:</u> Monitor patients more frequently for KOMZIFTI-associated adverse reactions. <u>Strong or moderate CYP3A inducers:</u> Avoid concomitant use of KOMZIFTI with strong or moderate CYP3A4 inducers. <u>PPIs:</u> Avoid concomitant use of KOMZIFTI with PPIs. <u>H2RAs:</u> Administer H2RAs either 10 hours before or 2 hours after KOMZIFTI administration. <u>Antacids:</u> Administer antacids either 2 hours before or 2 hours after KOMZIFTI administration. <u>QTc-prolonging drugs:</u> Avoid concomitant use of KOMZIFTI with other product(s) with a known potential to prolong the QTc interval. If concomitant use cannot be avoided, obtain ECGs when initiating, during concomitant use, and as clinically indicated. Interrupt KOMZIFTI if the QTc interval is > 500 ms or the change from baseline is > 60 ms.
Bridge between formulations	The Applicant utilized the same formulation throughout the clinical development process; therefore, bridging to the to-be-marketed formulation is not necessary.

Post-marketing Requirements (PMR) and Post-marketing Commitments (PMC)

FDA Table 22. Clinical Pharmacology PMR/PMCs

PMR or PMC	Rationale
PMR	Evaluate the impact of severe HI on ziftomenib PK
PMR	Evaluate the impact of severe RI on ziftomenib PK
PMR	Complete KO-MEN-001 Sub-study 2 to evaluate the impact of itraconazole (strong CYP3A and P-gp inhibitor) on ziftomenib PK
PMR	Evaluate the impact of BCRP inhibitors on ziftomenib PK
PMR	Complete KO-MEN-001 Sub-study 1 to evaluate the impact of ziftomenib on midazolam (sensitive CYP3A substrate) PK

Recommendations

The Office of Clinical Pharmacology has reviewed the information and data submitted in NDA 220305. This NDA is approvable from a clinical pharmacology perspective.

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6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The clinical pharmacology of ziftomenib was studied in patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) and healthy volunteers and assessed in modeling and simulation analyses. The objectives of the clinical pharmacology program were to evaluate the pharmacokinetics (PK), including absorption, metabolism, excretion, and the impact of extrinsic factors such as drug-drug interactions (DDIs), and food, as well as intrinsic factors such as hepatic and renal impairment.

Absorption: Ziftomenib is moderately permeable and is a substrate for BCRP and P-glycoprotein; however, PBPK modeling and clinical data have demonstrated that P-gp efflux or inhibition effect on ziftomenib exposure would be minimal and not clinically meaningful. Ziftomenib is rapidly absorbed ($T_{max} = 3.5$ hours) after oral administration in the fasted state, with an absolute bioavailability of 12.9%. A high-fat meal increased ziftomenib exposure by four times and delayed absorption. Co-administration with rabeprazole, a gastric acid-reducing agent, reduced ziftomenib exposure by up to 70%. PBPK modeling with esomeprazole demonstrated that staggering the PPI dose by 2 hours after ziftomenib had no effect on ziftomenib AUC and by ≥ 12 hours before ziftomenib may reduce AUC by 14%, which is not considered clinically meaningful. Thus, staggering PPI administration by 2 hours to 12 hours after the ziftomenib dose may have minimal impact on ziftomenib exposure.

Distribution: Ziftomenib is highly protein-bound ($>95\%$) in plasma, with a mean (%CV) apparent volume of distribution of 30100 L (98.4%). Ziftomenib has mean (%CV) half-life of 61.5 hours (26.3%) and a moderate accumulation upon once daily multiple-dose administration. Steady-state plasma levels are reached within 15 days.

Metabolism: Ziftomenib is primarily metabolized by CYP3A4 (60% of hepatic metabolism) and also by CYP1A2 and CYP2D6. Eight minor metabolites were identified, but ziftomenib remains the major component in plasma, accounting for 25-29% of total drug-related radioactivity.

Elimination: The mean (%CV) apparent oral clearance is 339 L/hour (88.6%). The main route of elimination is fecal (89.7%) with minimal renal excretion (0.525%).

Drug-Drug Interactions – Effect of Other Drugs on Ziftomenib PK:

Gastric Acid Reducing Agents: Administration of PPIs reduced ziftomenib AUC_{0-inf} by 53% and C_{max} by 70% in healthy volunteers. Modeling demonstrated that staggering the PPI dose by 2 hours after ziftomenib administration had no impact on ziftomenib AUC while staggering it by 12 hours resulted in a 14% reduction in ziftomenib AUC.

CYP3A4 Inhibitors: Modeling demonstrated weak to moderate changes in ziftomenib exposure with the CYP3A4 inhibitors. A strong CYP3A4 inhibitor (itraconazole) increases ziftomenib

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AUC 2.9 times and C_{max} 2.1 times, a moderate CYP3A4 inhibitor (fluconazole) increases ziftomenib AUC 1.8 times and C_{max} 1.6 times, and a weak CYP3A4 inhibitor (cimetidine) increases ziftomenib AUC by 36% and C_{max} by 37%. However, as safety exposure-response (E-R) analysis demonstrated that there were no statistically significant (ie, all p-values >0.05) E-R relationships with any ziftomenib model-predicted steady-state exposure measures and adverse events (AEs), the increase in ziftomenib exposure with CYP inhibitors is not considered to be clinically relevant. Ziftomenib can be co-administered with strong, moderate, or weak CYP3A4 inhibitors.

CYP3A4 Inducers: Modeling demonstrated that interactions with strong or moderate CYP3A4 inducers are likely to be moderate (AUC_{tau,ss} decrease by ≥50% – <80%). Interactions with weak CYP3A4 inducers are likely to be weak (AUC_{tau,ss} ≥20% – <50%). Co-administration of ziftomenib with strong or moderate CYP3A4 inducers should be avoided.

CYP1A2 Inhibitors and CYP2D6 Inhibitors: Modeling demonstrated a weak interaction between ziftomenib and either CYP1A2 or CYP2D6 inhibitors. Ziftomenib can be co-administered with CYP1A2 or CYP2D6 inhibitors.

Transporter Inhibitors: Ziftomenib is a substrate for P-gp and BCRP but not a substrate of BSEP or MRP2. Modeling demonstrated minimal to no impact of a P-gp inhibitor on the ziftomenib CL and volume. No clinically meaningful effect on ziftomenib is expected. Ziftomenib can be co-administered with P-gp inhibitors.

Drug-Drug Interactions – Effect of Ziftomenib on the PK of Other Drugs:

Based on modeling, no DDI was demonstrated with the CYP3A4 substrates midazolam or venetoclax or the UGT1A1 substrate raltegravir. Ziftomenib can be co-administered with sensitive CYP3A4 and UGT1A1 substrates.

Ziftomenib does not inhibit P-gp, BCRP, OAT1, OAT3, OCT2, MATE1, MATE2-K, OATP1B1, OATP1B3, BSEP, or MRP2.

Efficacy Exposure-Response (E-R) Analysis: No statistically significant relationships were found between steady-state ziftomenib exposure (AUC, C_{max} , C_{trough}) and efficacy endpoints (e.g., overall response rate or complete remission) in patients with R/R *NPM1*-m AML.

Safety Exposure-Response (E-R) Analysis: No statistically significant correlation was found between steady-state ziftomenib exposure (AUC, C_{max} , C_{trough}) and treatment-emergent adverse events (TEAEs) or severe adverse events (Grade 4+) in patients with R/R *NPM1*-m AML. Similarly, no meaningful relationship was observed for other safety endpoints. No covariates had a significant or clinically relevant effect on treatment-related adverse events (TRAEs).

Potential Effect on Cardiac Repolarization: The potential for QTc prolongation with ziftomenib was evaluated in an open-label Phase 1 study at doses ranging from 100 mg to 1000 mg once daily (0.17 to 1.7 times the approved recommended dosage) in 31 patients with relapsed or refractory AML. At the recommended KOMZIFTI dose of 600 mg once daily, no large mean

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changes in the QTc interval (>20 ms) were observed; the mean increase in QTcF was 8.25 ms in patients with relapsed or refractory AML.

The concentration-QTc analysis of ziftomenib showed that at a steady-state plasma concentration of 865 ng/mL, the upper bound of the 90% confidence interval for Δ QTcF is below 10 ms, indicating no clinically relevant QTc prolongation at these levels. At a higher concentration of 1380 ng/mL, the upper bound exceeds 20 ms, suggesting a larger change in QTc; however, this concentration is much higher than what is typically observed in clinical settings. Overall, the QTc analysis confirms that ziftomenib does not cause clinically significant QTc prolongation within its therapeutic concentration range. No significant effects were observed on heart rate, PR interval, or QRS interval, further supporting the safety of ziftomenib regarding cardiac repolarization and conduction.

The Applicant's Position:

The clinical pharmacology of ziftomenib has been studied in patients with R/R AML and in healthy volunteers, as well as assessed using modeling and simulation analysis. The clinical data along with NCA, PPK, ER, PBPK and concentration-QT analyses allowed for adequate characterization of ziftomenib ADME and PK, and assess intrinsic and extrinsic factors affecting ziftomenib exposure and impact on safety and efficacy of ziftomenib.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment of ziftomenib and metabolite (KO-739 and KO-516) PK. For a summary of FDA's assessment on the effect of intrinsic and extrinsic factors on ziftomenib PK, see Section 6.2.2.2.

For detailed information, see Section 6.3.1.

Exposure-Response (E-R): The FDA generally agrees with the Applicant's assessment of E-R analyses for safety and efficacy to support the proposed dosage for the target indication. For detailed information, see Section 14.4.3.

QTc prolongation: The FDA disagrees with the Applicant's assessment that ziftomenib has no clinically relevant effect on QTc. In R/R AML patients receiving ziftomenib 600 mg QD, a concentration-dependent increase in QTc was observed. For more detailed information, see Section 6.3.1.

Outstanding issues: There are several outstanding issues for which PMR/PMCs will be issued, as detailed in Section 6.2.2.3 and FDA Table 22.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

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Version date: March 1, 2024 (ALL NDA/BLA reviews)

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In Part 1a of Study KO-MEN-001, 30 patients with relapsed/refractory (R/R) AML were treated with ziftomenib in doses ranging from 50 to 1000 mg daily, establishing a maximum tolerated dose (MTD) of 800 mg/day. Based on safety, tolerability, PK and preliminary clinical activity observed in Part 1a, the 200 and 600 mg QD doses were selected for randomized comparison in Part 1b to determine the RP2D.

In Part 1b of Study KO-MEN-001, efficacy data from the randomized 200 mg and 600 mg doses of ziftomenib in patients with *NPM1*-m and *KMT2A*-r AML showed that the 600 mg QD dose had superior efficacy. No responses were reported at the 200 mg ziftomenib dose level, which, per protocol, led to the closure of this dose level to further enrollment due to futility. In contrast, the 600 mg ziftomenib dose level demonstrated clinical activity in both *NPM1*-m and *KMT2A*-r R/R AML. Here, the overall CR/CRh, composite complete remission (CRc), and ORR rates were 25.0%, 30.6%, and 33.3% respectively, with the majority of patients who were evaluated locally for MRD in each of the response categories also reaching MRD negativity. For Part 1b patients with *NPM1*-m AML treated with 600 mg ziftomenib, the durable CR and CRc rates were 35% and 40%, respectively. Safety data comparing the 200 mg and 600 mg doses of ziftomenib in patients with *NPM1*-m and *KMT2A*-r AML demonstrated no clear relationship between ziftomenib dose and safety profile.

PK data showed a three-fold increase in plasma exposure at steady state with the 600 mg dose compared to the 200 mg dose. E-R analysis indicated a trend toward higher response rates with increasing exposure in the *NPM1*-m patient population, though the results were not statistically significant. In patients with *NPM1*-m R/R AML, this increased exposure did not correlate with any additional safety concerns, including severe adverse events (AEs) or dose-limiting toxicity (DLT). Thus, the totality of clinical data and modeling supported 600 mg QD as the RP2D in R/R *NPM1*-m AML.

In the Phase 2 registrational portion of Study KO-MEN-001 in patients with R/R *NPM1*-m AML at 600 mg QD ziftomenib achieved the primary endpoint, with a CR/CRh rate of 21.7% (95% CI: 13.8 - 31.6), which demonstrated a statistically significant improvement ($p=0.0058$) in CR/CRh rate relative to the 12% historical control. The clinical benefit of 600 mg QD ziftomenib was further exemplified by its robust activity across all evaluated subgroups and key secondary endpoints. At 600 mg QD, the TEAEs were consistent with what is expected in an R/R AML population. The most common TEAEs included febrile neutropenia, differentiation syndrome (DS), and sepsis. Among these, 1.1% of febrile neutropenia cases were ziftomenib-related, all DS cases were linked to ziftomenib, and no sepsis cases were ziftomenib related. No deaths were attributed to ziftomenib-related TEAEs. E-R analysis demonstrated no statistically significant correlations between ziftomenib steady-state PK parameters (AUC, C_{max} or C_{trough}) and probability of response (efficacy or safety).

The Applicant's Position:

The recommended dosage of ziftomenib of 600 mg taken orally once daily was selected based on the totality of data demonstrating a favorable benefit-risk balance in Phase 1, where a range of

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doses were tested, and Phase 2. This dosing regimen is supported by the pharmacokinetic characteristics of ziftomenib, as well as its clinical efficacy with a favorable safety profile.

The integration of ziftomenib exposure-response findings for both efficacy and safety support the recommended dose of 600 mg QD dose of ziftomenib as the optimal regimen, maximizing efficacy in patients with *NPM1*-m R/R AML while maintaining a favorable safety profile.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position that the totality of the data support a favorable risk-benefit profile for ziftomenib 600 mg QD in patients with *NPM1*-m R/R AML. The 600 mg dosage demonstrated improved activity versus the 200 mg dosage (CR + CRh 25% vs 0%). The dose-response (D-R) and E-R safety relationships for ziftomenib are relatively flat, supporting the proposed 600 mg dose.

For more detailed information, see Sections 6.3.2.1 and 6.3.2.2.

6.2.2.2. Therapeutic Individualization

Data:

Impact of intrinsic factors on ziftomenib pharmacokinetics (PK) was assessed in the population PK model (PPK) analysis. Disease state (AML patient vs. healthy volunteers) was identified as a statistically significant covariate. However, since dose optimization was specifically conducted in patients with *NPM1*-m AML, no further dose adjustments were required. The PPK analysis indicated that intrinsic factors such as age (ranging 18 to 86 years), body weight, height, BMI, BSA, eGFR, serum creatinine, bilirubin, albumin, ALP, ALT, AST, sex, race, ethnicity, mutation type, mild or moderate renal impairment, and mild or moderate hepatic impairment did not significantly affect the PK of ziftomenib. Therefore, no therapeutic individualization or dose adjustment is needed based on these factors.

Ziftomenib has not been studied in pediatric patients.

The PPK analysis demonstrated that mild (n=32, 17%) and moderate (n=5, 2.7%) hepatic impairment, as classified by the NCI Organ Dysfunction Working Group, did not significantly affect ziftomenib exposure. The effect of severe hepatic impairment on ziftomenib's PK has not been assessed (no patient enrolled in study KO-MEN-001).

Given the low renal excretion of ziftomenib (only 0.525% of the radioactive dose was excreted in urine) demonstrated in the completed mass balance study (KO-MEN-005), renal impairment is not expected to significantly influence ziftomenib's PK, which is confirmed by the PPK analysis showed that mild (n=72, 38.3%) and moderate (n=21, 11.2%) renal impairment did not notably affect the PK parameters of ziftomenib. The impact of severe renal impairment (eGFR $\leq$ 29 mL/min) on ziftomenib's PK was not investigated (no patient enrolled in study KO-MEN-001).

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A high-fat meal increased ziftomenib exposure by four times and delayed absorption; therefore, ziftomenib is recommended to be administered in the fasted state.

Co-administration with rabeprazole, a gastric acid-reducing agent, reduced ziftomenib exposure by up to 70%. PBPK modeling with esomeprazole demonstrated that staggering the PPI dose by 2 hours after ziftomenib had no effect on ziftomenib AUC and by ≥ 12 hours before ziftomenib may reduce AUC by 14%, which is not considered clinically meaningful. Thus, staggering PPI administration by 2 hours to 12 hours after the ziftomenib dose would have minimal impact on ziftomenib exposure. No adjustments for ziftomenib are needed with co-administration of gastric acid reducing agents.

Additional extrinsic factors were the subject of PPK and PBPK analysis which indicated that interactions with strong or moderate CYP3A4 inducers are expected to cause a reduction in ziftomenib exposure ($AUC_{\tau,ss}$ decreasing by $\geq 50\%$ to $< 80\%$). Interactions with weak CYP3A4 inducers are likely to result in a smaller effect, with $AUC_{\tau,ss}$ decreasing by $\geq 20\%$ to $< 50\%$. Strong CYP3A4 inhibitors have been identified as a significant covariate on ziftomenib CL, leading to an approximately two-fold increase in ziftomenib exposure, with C_{min} , C_{max} , and AUC values being 2.44-, 1.96-, and 2.18-fold higher, respectively. Despite this increase in exposure, safety and exposure-response (E-R) analysis showed no statistically significant relationships (all $p > 0.05$) between ziftomenib model-predicted steady-state exposure measures (AUC_{ss} , $C_{max,ss}$, and $C_{min,ss}$) and adverse events (AEs). As a result, the increase in ziftomenib exposure with CYP3A4 inhibitors is not considered clinically relevant, and no dose adjustment is required when ziftomenib is co-administered with strong or moderate CYP3A4 inhibitors. No DDI was predicted with the CYP2D6 inhibitor bupropion. Interactions with strong CYP1A2 inhibitors (fluvoxamine) are likely to be weak.

Coadministration of strong and moderate CYP3A inducers is to be avoided.

The Applicant's Position:

The recommended dosage of ziftomenib is 600 mg taken orally once daily in the fasted state. No dose adjustment is required based on age, body weight, sex, race, mild or moderate renal or hepatic impairment, co-administration with strong or moderate CYP3A4 inhibitors or with CYP1A2 or CYP2D6 inhibitors. The impact of severe renal or hepatic impairment on ziftomenib PK has not been studied. Co-administration of ziftomenib with strong or moderate CYP3A inducers should be avoided, and (b) (4)

The FDA's Assessment:

Intrinsic factors:

The FDA agrees with the Applicant's positions that no dosage adjustment is required based on age (18 to 86 years), sex (51% female), race (75% White, 5.3% Black or African American, 3.2% Asian), ethnicity (6.3% Hispanic or Latino), mild (bilirubin less than or equal to ULN and AST greater than ULN or bilirubin less than or equal to 1.5 x ULN) or moderate (bilirubin 1.5 to

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3 x ULN) hepatic impairment, or mild (CL_{Cr} 30 to 59 mL/min) or moderate (CL_{Cr} 60 to 89 mL/min) renal impairment. For more detailed information, see Section 6.3.2.3.

Extrinsic factors:

The FDA generally agrees with the following Applicant positions:

- Administer ziftomenib in the fasted state (at least 1 hour before or 2 hours after a meal);
- No dosage adjustment is required based on concomitant use of CYP1A2 or CYP2D6 inhibitors;
- Concomitant use of strong or moderate CYP3A inducers should be avoided
- H2RAs should be administered with staggered dosing (10 hours before or 2 hours after KOMZIFTI administration);
- Dose adjustment recommendation is not required for sensitive CYP3A substrates:
 - Dose adjustment of sensitive CYP3A substrates is not warranted when used concomitantly with ziftomenib administered alone, as it is a weak CYP3A inhibitor.
 - When the concomitant ziftomenib is administered with strong or moderate CYP3A inhibitors, the dose adjustment guidance of sensitive CYP3A substrates will follow the strong or moderate CYP3A inhibitors.

However, the FDA has comments regarding the following Applicant positions:

- While the FDA agrees that no dosage adjustment is required based on concomitant use of strong or moderate CYP3A inhibitors, the FDA does not agree with the Applicant's assessment that the ~2-fold increase in ziftomenib exposure observed when coadministered with these agents is not considered clinically relevant. Therefore, the FDA recommends additional safety monitoring in patients receiving strong or moderate CYP3A inhibitors.
- The FDA disagrees with the Applicant's position that (b) (4)

Therefore, the FDA recommends that concomitant use of PPIs should be avoided.

- The FDA generally agrees with the Applicant's position that staggered dosing with antacids is appropriate; however, the FDA recommends that antacids should be administered either 2 hours before or after KOMZIFTI administration consistent with the short duration of action of antacids.

For more detailed information, see Section 6.3.2.4.

6.2.2.3. Outstanding Issues

Data:

N/A

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The Applicant's Position:

N/A

The FDA's Assessment:

There are several outstanding clinical pharmacology issues for which PMRs will be issued, including assessing the effect of severe RI, severe HI, and concomitant administration with BCRP inhibitors on ziftomenib PK. Additionally, PMRs will be issued for the Applicant to complete KO-MEN-001 Sub-studies 1 and 2 evaluating the PK of ziftomenib when coadministered with itraconazole and the PK of midazolam when coadministered with ziftomenib (FDA Table 22).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Applicant Table 2: Applicant - Ziftomenib Highlights of Clinical Pharmacology

Therapeutic dose and exposure	The proposed therapeutic dose is 600 mg QD. Mean (%CV) C_{max} = 184 ng/mL (165.5%) and AUC_{0-24} = 2290 ng/mL*hr (137.5%) at single dose (Cycle 1 Day 1 of Part 1b of KO-MEN-001) based on non-compartmental analysis. Mean (%CV) C_{max} = 881 ng/mL (111.8%) and AUC_{0-24} = 12200 ng/mL*hr (151.9%) at steady state (Cycle 2 Day 1 of Part 1b of KO-MEN-001) based on non-compartmental analysis.	
Maximum tolerated dose	Clinical MTD in patients: 800 mg QD Mouse STD10: STD10 >120 mg/kg/day but <400/200 mg/kg/day Dog HNSTD: 60 mg/kg/day (28-day toxicology study) Dog HNSTD: 20 mg/kg/day (13-week toxicology study)	
Maximum dose tested	Single Dose	1000 mg QD (n=1)
	Multiple Dose	1000 mg QD for consecutive 28-day cycles in (n=1)
Exposures Achieved at Maximum Tested Dose	Single Dose	C_{max} =512 ng/mL and AUC_{0-24} =7230 ng/mL*hr
	Multiple Dose	C_{max} =2357 ng/mL and AUC_{0-24} =55199 ng/mL*hr

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Range of linear PK	50 – 600 mg QD (based on Cycle 1 Day 1 AUC ₀₋₂₄)	
Accumulation at steady state	Approximately 5-fold accumulation after 28 days of dosing 600 mg QD.	
Metabolites	Active metabolites: KO-516 and KO-739 Activity for safety and efficacy (e.g., receptor binding): The IC₅₀ for inhibiting binding of menin to MLL(KMT2A)-derived peptide in biochemical assays are 37 nM, 27 nM and 50.5 nM for ziftomenib, KO-516, and KO-739, respectively. Both KO-516 and KO-739 have been determined to be minor metabolites in a human ADME study (KO-MEN-005).	
Absorption	Absolute/Relative Bioavailability	Mean (%CV) absolute oral bioavailability (%F) = 12.9% (115%) under fasting conditions at 400 mg (KO-MEN-005)
	T _{max}	Median (range) for ziftomenib is 3.5 h (1.5-24 h) at 400 mg dose (KO-MEN-005)
Distribution	Vd/F or Vd	Mean (%CV): 30100 L (98.4%) at 400 mg (KO-MEN-005)
	% bound	Mean (%CV): >99% bound
Elimination	Route	Ziftomenib is primarily excreted in feces (89.7% of radioactive dose), and trace amounts in urine (0.525% of radioactive dose) after oral administration to healthy volunteers. Ziftomenib underwent minor metabolism with all circulating metabolites being minor (% of drug related exposure for KO-739 was 3.39% and 9.18%, and for KO-516 was 2.3% and 2.72%) (KO-MEN-005).
	Terminal t _{1/2}	Mean (%CV): 61.5 h (26.3%) for ziftomenib
	CL/F or CL	Mean (%CV): 339 L/hr (88.6%)
Intrinsic Factors	Age	Population-PK analysis of adult subjects demonstrated no effect of age on ziftomenib PK.

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	Sex	Population-PK analysis demonstrated no effect of sex on ziftomenib PK.
	Race	Population-PK analysis demonstrated no effect of race on ziftomenib PK.
	Hepatic & Renal Impairment	Population-PK analysis demonstrated no significant effect of mild or moderate hepatic and renal impairment on ziftomenib PK. Additionally, in study KO-MEN-005, only 0.525% of the ziftomenib dose was recovered in urine, suggesting that ziftomenib renal elimination is minimal. So, renal impairment is not expected to have any effect on ziftomenib exposure.
Extrinsic Factors	Drug interactions	Rabeprazole, a proton-pump inhibitor (PPI), reduced ziftomenib AUC by approximately 3-fold (KO-MEN-003). Formal clinical assessment of the effect of CYP3A4 inhibitor on ziftomenib exposure has not been completed yet. PBPK modeling of the relative impact of strong inhibitors of CYP3A4, on ziftomenib Cycle 1 Day 1 (C1D1) C_{max} and AUC_{tau} in Study KO-MEN-001, were used to estimate the f_mCYP3A4. A conservative estimate of CYP3A4 contribution to the overall hepatic metabolism of ziftomenib was 60%, based on clinical data. The remaining hepatic metabolism (40%) was attributed equally to CYP1A2 and CYP2D6 (f_mCYP = 20% for each isoform). The verified PBPK model was applied to predict interactions between ziftomenib and strong, moderate and weak CYP3A4 inhibitor; strong, moderate and weak CYP3A4 inducer; CYP2D6 and CYP1A2 inhibitor. The model demonstrated that itraconazole (strong CYP3A4 inhibitor), fluvoxamine

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		(CYP1A2 inhibitor) and bupropion (CYP2D6 inhibitor) increased ziftomenib AUC by 2.86-fold, 1.55-fold, and 1.20-fold, respectively.
	Food Effects	High fat meal increased ziftomenib AUC and C_{max} by approximately 4-fold (KO-MEN-003).
Expected High Clinical Exposure Scenario	There is an approximately 4-fold increase in ziftomenib C_{max} and AUC when taken with high fat meal. Hence the expected high C_{max-ss} is approximately 3524 ng/mL at 600 mg QD. However, ziftomenib is recommended to be taken in fasted state.	
Nonclinical Safety Pharmacology Studies (S7B)	In a GLP compliant <i>in vitro</i> hERG channel assay (KO-TOX-0023), ziftomenib IC₅₀ for inhibitory effect on hERG was 0.066 μM. At the RP2D of 600 mg QD, the steady state C_{max} was 881 ng/mL (1.22 μM). The expected high clinical exposure at this dose with high fat meal is expected to be approximately 4.88 μM. Given that ziftomenib has >99% protein binding, the free drug C_{max-ss} will be approximately 0.049 μM, which is 1.3-fold lower than the IC₅₀. In a GLP complaint CV assessment in conscious radiotelemetrized beagle dogs (KO-TOX-0022) 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.	
Clinical Cardiac Safety	Monotherapy (KO-MEN-001): Based on concentration-QT interval corrected for heart rate (QTcF) analysis (Study KO-PK-0003) of ECGs from 31 patients in Study KO-MEN-001 Parts 1a and 1b, a ΔQTcF increase with 90% upper confidence interval (UCI) exceeding 10 ms and 20 ms can be predicted for ziftomenib plasma concentration of approximately 865 ng/mL and 1380 ng/mL, respectively. At steady state, ziftomenib mean C_{max} was 881 ng/mL at 600 mg once daily (QD), demonstrating that ziftomenib is not expected to have a clinically significant effect on QTc prolongation. Categorical analysis demonstrated that there were no QTcF prolongation >480 ms, >500 ms, or ΔQTcF >60 ms. Ziftomenib also had no clinically significant effect on heart rate or on cardiac conduction (ie, the PR or QRS interval). In summary, the results from the cardiodynamic	

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	evaluation demonstrated no clinically relevant effect of ziftomenib on QTc or other ECG parameters.

The Applicant's Position:

The clinical pharmacology of ziftomenib was assessed in in vitro studies, in clinical studies in patients with R/R AML and healthy volunteers, as well as in modeling and simulation analyses. The objectives of the clinical pharmacology program were to evaluate the pharmacokinetics (PK), including absorption, metabolism, excretion, and the impact of extrinsic factors such as drug-drug interactions (DDIs), and food, as well as intrinsic factors such as hepatic and renal impairment. Exposure-response and -safety relationships were modeled using data from Study KO-MEN-001, as was a concentration-QT evaluation.

Based on the extent and results of these studies and assessments, the clinical pharmacology of ziftomenib was well characterized to inform the overall pharmacokinetic profile and provide guidance for using ziftomenib in the proposed USPI.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment that ziftomenib PK are adequate to inform the overall PK profile and provide guidance for ziftomenib use.

General PK

Exposure: The FDA does not agree with the Applicant's position regarding mean exposure, as it does not account for coadministration of CYP3A inhibitors, which were commonly used in KO-MEN-001, on ziftomenib PK.

The FDA assessed steady state PK of ziftomenib (C2D1) at 600 mg (the approved dosage) when administered with strong CYP3A inhibitors or without CYP3A inhibitors. The FDA analysis utilized population PK (PopPK)-derived Cycle 2 Day 1 C_{max} and AUC values. Coadministration of a strong CYP3A inhibitor was defined as any administration of the strong CYP3A inhibitor within 3 days prior to the C2D1 ziftomenib PK sample. Patients with concomitant PPI use on the day of ziftomenib administration were excluded from the analysis given the known DDI observed with PPI administration.

Steady-state maximum plasma concentration (C_{max} ; $C_{max,ss}$) was 617 (33%) ng/mL when co-administered with strong CYP3A inhibitors, compared to 288 (41%) ng/mL when administered without strong CYP3A inhibitors. Steady-state area under the concentration-time curve at last sampling time (AUC; $AUC_{last,ss}$) was 13,185 (36%) ng*h/mL when co-administered with strong CYP3A inhibitors, compared to 5,512 (48%) ng*h/mL when administered without strong CYP3A inhibitors.

Dose proportionality: The FDA does not agree with the Applicant's assessment of dose-proportionality over 50 to 600 mg due to the limited sample size at lower doses (i.e., n=1 for

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each 50 mg and 100 mg) and confounded by DDIs (i.e., coadministration with CYP3A inhibitors and ARAs) in the Phase 1a dose escalation cohorts.

The FDA assessed dose proportionality of single-dose (Cycle 1 Day 1) PK in the Phase 1a/b dose escalation and expansion cohort with patients coadministered strong CYP3A inhibitors but not ARAs. Cohorts with $n \geq 3$ per dose were evaluated. Dose-proportionality could not be assessed in patients not coadministered strong CYP3A inhibitors due to an insufficient number of patients at each dose level.

The power model slope estimates (95% CI) were 0.92 (-0.06, 1.90) for AUC at 24 hours (AUC_{24}), 1.06 (0.14, 1.99) for AUC over the dosing interval (AUC_t), and 0.74 (0.18, 1.67) for C_{max} . AUC was dose-proportional and C_{max} was slightly less than dose-proportional over a dose range of 200 mg (0.3 times the approved dose) to 600 mg (the approved dose).

Accumulation: The FDA recommends reporting accumulation based on a comparison of single-dose versus steady-state exposures observed in the 600 mg QD phase 1b expansion cohort, which indicates an approximately 3-fold accumulation after 28 days of dosing (C_{max} accumulation ratio [AR]=2.7, AUC_{24} AR=3.4)

Absorption, Distribution, Metabolism, Elimination, Transport

Absorption: The FDA agrees with the Applicant's assessment that ziftomenib absolute BA is low (13%), despite moderate in vitro permeability (apparent permeability [P_{app}]= 2.69×10^{-6} cm/s).

The FDA recommends reporting time to C_{max} (T_{max}) based on that observed at Cycle 2 Day 1 in the 600 mg QD phase 1b expansion cohort, for which T_{max} was 4.1 hours (0.5 to 8.2 hours).

Distribution: The FDA agrees with the Applicant's assessment that ziftomenib is > 99% bound to plasma proteins (mainly albumin) with blood-to-plasma partition coefficient ($K_{B/P}$)=0.60 to 0.73 and apparent volume of distribution (V_z/F)=30,100 L (98%).

Metabolism: The FDA agrees with the Applicant's assessment that ziftomenib is primarily metabolized by CYP3A, and the parent compound accounts for the majority of circulating drug-related exposure.

Elimination: The FDA does not agree with the Applicant's assessment of the elimination PK values, because it does not account for coadministration of CYP3A inhibitors, which were commonly used in KO-MEN-001.

The FDA conducted the following assessment to characterize steady state (Cycle 2 Day 1) $t_{1/2}$ and apparent oral clearance (CL/F) of ziftomenib when administered with strong CYP3A inhibitors or without CYP3A inhibitors. The FDA analysis utilized PopPK-derived Cycle 2 Day 1 PK values. Coadministration of a strong CYP3A inhibitor was defined as any administration of the strong CYP3A inhibitor within 3 days prior to the Cycle 2 Day 1 ziftomenib PK sample. Patients with concomitant PPI use on the day of ziftomenib administration were excluded from the analysis given the known DDI observed with PPI administration.

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Based on the FDA analysis, elimination half-life ($t_{1/2}$) was 190 (23%) hours when coadministered with strong CYP3A inhibitors and 94 (21%) hours when administered without CYP3A inhibitors. CL/F was 42 (29%) L/h when coadministered with strong CYP3A inhibitors and 101 (27%) L/h when administered without CYP3A inhibitors

Excretion: The FDA agrees with the Applicant's position that the role of renal elimination of ziftomenib is minimal, given that 0.5% total radioactivity was excreted in the urine and renal clearance (CL_R) was low (0.1 L/h).

The FDA does not agree with the Applicant's position that “ (b) (4)

In study KO-MEN-005, 86% of total radioactivity was excreted in the feces, with 73% as unchanged drug. The majority of unchanged drug in the feces following a single oral dose of 400 mg [^{14}C]-ziftomenib likely represents unabsorbed drug due to low bioavailability.

Transport: The FDA agrees with the Applicant's assessment that ziftomenib is a substrate of P-gp and BCRP *in vitro*, which likely play a role in ziftomenib absorption given low bioavailability despite moderate permeability. Ziftomenib is not a substrate of OATP1B1, OATP1B3, BSEP, or MRP2 *in vitro*. It is unlikely that ziftomenib is a substrate of renal transporters (e.g., OAT1/3, OCT2) due to the minimal role of renal clearance in ziftomenib elimination.

Intrinsic & Extrinsic Factors

For detailed information on the FDA's Assessment of intrinsic factors, see Section 6.3.2.3. For detailed information on the FDA's Assessment of extrinsic factors, see Section 6.3.2.4.

PD

The FDA agrees with the Applicant's assessment that the *in vitro* menin-KMT2A IC_{50} for ziftomenib is 37 nM *in vitro*. The Applicant did not submit clinical PD data.

QTc Prolongation: The FDA does not with the Applicant's assessment that ziftomenib has no clinically relevant effect on QTc.

The FDA evaluated the effect of KOMZIFTI on the QTc interval in n=133 R/R AML patients treated at 600 mg QD. Ziftomenib exhibited a concentration-dependent increase in QTc interval with largest mean increase in QTc interval predicted to be 7.7 ms (upper confidence interval [CI]=12.6 ms). 8% (n=10) patients had QTc > 500 ms and increase in QTc > 60 ms over baseline.

Metabolite PK/PD

PK: The FDA agrees with the Applicant's assessment that the major circulating metabolites KO-516 and KO-739 are formed via CYP3A-mediated metabolism. After a single dose of ziftomenib, KO-516 and KO-739 were minor metabolites (metabolite-to-parent ratio [M:P] for AUC_{inf} approximately equal to 0.1 and 0.2, respectively).

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However, the FDA disagrees that ^{(b) (4)} given that exposure at steady-state (Cycle 2 Day 1) following 600 mg QD dosing is comparable to that of ziftomenib due to high accumulation ($C_{max}=764$ ng/mL, $AUC_{24}=12,200$ ng*h/mL, AR ~14).

Efficacy: The FDA agrees with the Applicant's assessment that neither KO-516 nor KO-739 are likely to contribute meaningfully to ziftomenib efficacy. The menin-KMT2A binding half-inhibitory concentration (IC_{50}) for KO-516 and KO-739 are 27 nM and 50 nM, respectively. The activity of KO-516 is comparable to ziftomenib ($IC_{50}=37$ nM); however, KO-516 is unlikely to significantly contribute to efficacy given relatively low exposure (M:P = 0.14 at steady-state). KO-739 is unlikely to significantly contribute to efficacy given relatively low activity.

Safety: The FDA agrees with the Applicant's assessment that 13-week repeat-dose toxicology study in dogs (KO-TOX-0013) provides safety coverage for metabolites KO-516 and KO-739.

DDI Potential: The FDA agrees with the Applicant's assessment that KO-739 is metabolized by CYP3A and CYP2D6 *in vitro* and that based on *in vitro* values and assuming similar f_u to ziftomenib, KO-739 is not expected to be a clinically relevant inhibitor of CYP2C8, CYP2C9, CYP3A, or inducer of CYP1A2. The Applicant did not provide data regarding metabolism or DDI potential given KO-516 is a minor metabolite.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes, the clinical pharmacology program provides supportive evidence of effectiveness for ziftomenib, particularly at the 600 mg QD dose. The totality of clinical data and modeling and simulation described in Section 6.2.1 supports the effectiveness of the proposed dosing regimen. E-R analysis showed a lack of clinically significant relationship between exposure and efficacy, thus demonstrating that exposures achieved were adequate for robust efficacy.

The FDA's Assessment:

The 600 mg dosage is supported primarily by the efficacy data in the dose expansion phase of KO-MEN-001 (Phase 1 Part 1b), which demonstrated improved activity at 600 mg versus 200 mg (CR + CRh 25% vs 0%). Although there was no significant E-R efficacy relationship, this is likely an artifact of the limited sample size at dose levels other than 600 mg and low CR + CRh overall.

Overall CR + CRh was 21% in *NPM1-m R/R AML* (n=112, Phase 1b EAS + Phase 2).

D-R Analysis: In Phase 1 Part 1a (all comers), there was no clear D-R relationship for CR + CRh (0% at 50 mg [n=1], 100% at 100 mg [n=1], 17% at 200 mg [n=6], and 0% at 400 to 1000 mg [n=1 to 11 per cohort]).

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In Phase 1 Part 1b (*NPM1-m* and *KMT2A-r*), no CR + CRh responses were observed at the 200 mg dosage (n=17), leading to the 200 mg cohort being closed for futility. In comparison, the CR + CRh rate was 25% at the 600 mg dosage (n=36).

In Phase 2 (*NPM1-m*), the CR + CRh rate at 600 mg was 19% (n=92), which is similar to that observed in Phase 1 Part 1b.

E-R Analysis: The Applicant conducted E-R analyses for efficacy in n=100 *NPM1-m* R/R AML patients. The Applicant assessed several combinations of response endpoints, including complete/partial response (CR, CRmrd-, or CRh) and complete/partial response (CR, CRmrd-). No significant relationship was observed between ziftomenib exposure and response. However, the flat E-R analyses were likely impacted by the limited patient sample size at dose levels other than 600 mg (n=1 at 50, 100, and 100 mg; n < 12 at 400 and 800 mg; n= 23 at 200 mg) and low CR/CRh overall [Section 14.4.3].

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes, the proposed dosing regimen of 600 mg QD demonstrated efficacy in the indicated population with a manageable safety profile in Study KO-MEN-001. The ziftomenib 600 mg QD dose demonstrated superior efficacy compared to the 200 mg QD dose in the comparative Phase 1 evaluation leading to the recommended phase 2 dose selection. In the Phase 2 registrational study the robust efficacy and manageable safety profile of 600 mg QD dose was confirmed in R/R *NPM1-m* AML patients, as described in Section 6.2.2.1. Clinical evaluation indicated a food effect and interaction with proton-pump inhibitors, however, additional modeling informed that staggered administration of PPIs would not have a clinically meaningful effect. The PPK analyses did not reveal any clinically meaningful effect of intrinsic factors such as age (ranging 18 to 86 years), body weight, height, BMI, BSA, eGFR, serum creatinine, bilirubin, albumin, ALP, ALT, AST, sex, race, ethnicity, mutation type, mild or moderate renal impairment, and mild or moderate hepatic impairment. Importantly, modeling also indicated there was no clinically meaningful effect on ziftomenib exposure with co-administered CYP inhibitors. Thus, ziftomenib dose adjustment is not required for these intrinsic and extrinsic factors. Ziftomenib at the recommended dose of 600 mg QD demonstrates a favorable benefit-risk profile for patients with R/R *NPM1-m* AML.

The FDA's Assessment:

The FDA agrees with the recommended dose and regimen of 600 mg daily based on assessments of efficacy, safety, and PK.

Of note, dose-finding was performed irrespective of coadministration of CYP3A-inhibiting azole antifungals. Coadministration of strong CYP3A-inhibiting azoles was widespread for KO-MEN-001 participants. Therefore, D-R and E-R relationships are driven primarily by ziftomenib

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efficacy, safety, and PK/PD in patients receiving strong CYP3A-inhibiting azoles [Section 6.3.2.4].

Efficacy

See Section 6.3.2.1.

Safety

The D-R and E-R safety relationships for ziftomenib were flat, supporting the proposed 600 mg dose. Of note, the proposed dose is 1 dose level below the maximum tolerated dose (MTD) of 800 mg.

D-R Analysis: In Phase 1 Part 1a, there were no clear D-R relationships for treatment-emergent adverse event (TEAE) (97%), grade ≥ 3 TEAE (83%), grade 5 TEAE (20%), serious adverse event (SAE, 77%), dose interruption (23%), or treatment discontinuation (23%). The dose-limiting toxicities (DLTs) included differentiation syndrome (n=1 at 1000 mg) and pneumonitis (n=1 at 400 mg). 800 mg was determined to be the MTD following a DLT in 1 patient at 1000 mg.

In Phase 1 Part 1b, there were no clear D-R relationship between 200 mg and 600 mg for TEAE (100% at both doses), grade ≥ 3 TEAE (94% at both doses), grade 5 TEAE (41 vs 28%), SAE (82% vs 83%), dose interruption (41 vs 44%), treatment discontinuation (12 vs 28%), febrile neutropenia (41% vs 17%), or differentiation syndrome (35% vs 31%). There were no clear D-R relationships for DLTs, including differentiation syndrome (17% vs 14%) and cardiomyopathy (0% vs 3.4%).

E-R Analysis: The Applicant conducted E-R analyses for safety in 174 patients. There were no significant relationships between ziftomenib exposure and grade ≥ 3 TEAE; grade ≥ 4 TEAE; grade ≥ 3 TRAE; grade ≥ 4 TRAE; grade ≥ 3 anemia, febrile neutropenia, neutropenia, pneumonia, sepsis, thrombocytopenia, differentiation syndrome; or treatment-related differentiation syndrome [Section 14.4.3].

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:

No, there is no dose adjustment needed based on modeling assessment of intrinsic factors.

The effects of age, body weight, height, BMI, BSA, sex, race, ethnicity, AML mutation, eGFR, serum creatinine, bilirubin, albumin, ALP, ALT, AST, renal impairment mild or moderate ((CLCr) 50-80 and (CLCr) 30-50 mL/min) or hepatic impairment mild or moderate (Child-Pugh Class A and B) were evaluated by population PK modeling. None of these covariates had an impact on ziftomenib PK, as discussed in Section 6.2.1. The effect of severe hepatic impairment

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(Child-Pugh Class C) or severe renal impairment ($CL_{Cr} \leq 29$ mL/min) on ziftomenib pharmacokinetics has not been studied.

The FDA's Assessment:

The FDA generally agrees that no clinically significant differences in the PK of ziftomenib were observed based on the following intrinsic factors: age (18 to 86 years), body weight (41 to 135 kg), height (142 to 193 cm), body mass index (BMI, 18.0 to 52.7 kg/m²), BSA (1.40 to 2.46 m²), sex (51% female), race (75% White, 3.2% Asian, 5.3% Black of African American), ethnicity (6.3% Hispanic or Latino, 78.5% not Hispanic of Latino), AML mutation (no mutation, *NPM1*-m, *KMT2A*-r, or others), serum creatinine (SCr, 0.39 to 2.00 mg/dL), mild (CL_{Cr} 30 to 59 mL/min) to moderate (CL_{Cr} 60 to 89 mL/min) renal impairment, bilirubin (0.2 to 2.3 mg/dL), albumin (25 to 50 g/L), alkaline phosphatase (ALP, 26 to 748 U/L), alanine transaminase (ALT, 7 to 99 U/L), AST (9 to 69 U/L), or mild (bilirubin less than or equal to ULN and AST greater than ULN or bilirubin less than or equal to 1.5 x ULN) to moderate (bilirubin 1.5 to 3 x ULN) hepatic impairment. For more detailed information, see Section 14.4.2.

The effect of severe renal (CL_{Cr} less than 30 mL/min) and hepatic (bilirubin greater than 3 x ULN) impairment have not been studied; therefore, it is unknown if therapeutic individualization will be required for these patients and PMRs will be issued (FDA Table 22).

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

Based on clinical evaluation, there is a food effect and interaction with PPIs. To minimize the impact of food on ziftomenib absorption, it is recommended that ziftomenib be taken on an empty stomach to ensure consistent absorption and avoid potential overexposure. (b) (4)

While co-administration of ziftomenib with strong or moderate CYP3A4 inducers should be avoided, based on modeling discussed in Section 6.2.1, no clinically meaningful interaction is indicated with strong, moderate or weak CYP3A4, CYP1A2, or CYP2D6 inhibitors.

The FDA's Assessment:

Food Effect

The FDA agrees with the Applicant's position that ziftomenib should be taken on an empty stomach (1 h before or 2 h after a meal).

Administration of ziftomenib with a high-fat meal increases ziftomenib exposure by ~4-fold (C_{max} =123 ng/mL [53%] vs 502 ng/mL [43%]; AUC from 0 to infinity [AUC_{inf}]=2,490 ng*h/mL [58%] vs 10,300 ng*h/mL [53%]). Exposure of metabolites KO-516 and KO-739 also increased ~4-fold. Additionally, fasted administration is consistent with ziftomenib administration during

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KO-MEN-001 (as of Protocol Version 2 [02/22/2019]).

Metabolic DDI

Strong and moderate CYP3A inhibitors: The FDA generally agrees with the Applicant's position that ziftomenib can be administered with strong CYP3A inhibitors without dose adjustment. However, the FDA recommends increased safety monitoring for these patients.

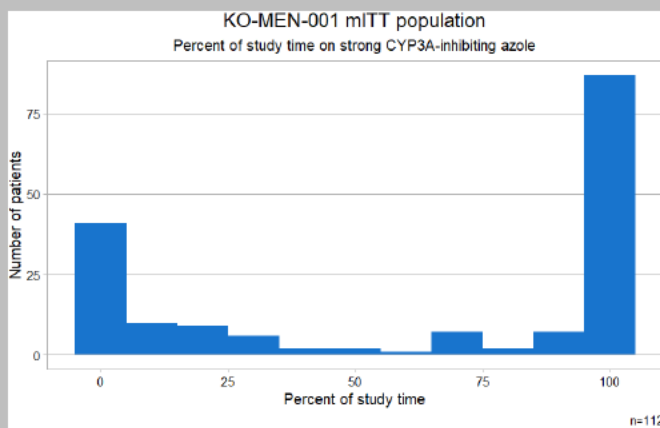
CYP3A-inhibiting azole use: Coadministration of strong CYP3A inhibitors was permitted in KO-MEN-001, as azole antifungals are standard of care in AML. The distribution of strong CYP3A-inhibiting azole use in the KO-MEN-001 mITT population is shown in

FDA Figure 2, and Swimmer plots for azole use in patients who never received a strong CYP3A-inhibiting azole is shown in FDA Figure 3.

The majority of patients receiving a strong CYP3A-inhibiting azole received posaconazole. Most patients received strong CYP3A-inhibiting azoles for the majority (over 75%) of study time, with a smaller plurality of patients receiving a strong CYP3A-inhibiting azole for 0 to 10% of study time. Of the n=15 patients who were never on strong CYP3A-inhibiting azoles, n=4 received other CYP3A-inhibiting azoles on study, including fluconazole and isavuconazole. Therefore, the subset of patients who never received any CYP3A-inhibiting azoles was small.

Given the widespread use of strong CYP3A-inhibiting azoles in KO-MEN-001, D-R and E-R relationships are driven primarily in the presence of strong CYP3A-inhibiting azoles.

FDA Figure 2. Percent of Study Time on Strong CYP3A-inhibiting Azole in KO-MEN-001 mITT Population



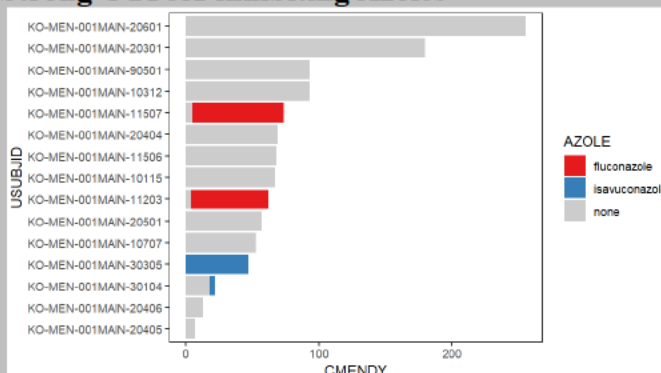
Source: Reviewer analysis.

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FDA Figure 3. Swimmer Plots for Azole Administration in n=16 Patients in mITT Population Never on Strong CYP3A-inhibiting Azoles



Source: Reviewer analysis.

PK: The FDA evaluated the effect of strong CYP3A-inhibiting azole use on ziftomenib PK in patients not receiving PPIs (to control for other known DDIs), as shown in

FDA Table 23. In patients receiving strong CYP3A-inhibiting azoles, ziftomenib single-dose C_{max} and AUC were 23% and 76% higher, respectively, and steady-state C_{max} and AUC were 118% and 145% higher, respectively, than in patients not receiving azoles. Although variability in the FDA analysis was high, results were consistent with PopPK and physiologically-based PK (PBPK) analyses submitted by the Sponsor demonstrating ~2-fold increase in ziftomenib exposure at steady state [Section 14.4.2, 14.4.4].

FDA Table 23. Ziftomenib PK Parameters with Strong CYP3A Inhibitor Use

Single-dose (C1D1) ^a			
	No CYP3A inhibitor (n=8)	Strong CYP3A-inhibiting azole (n=12)	GMR
Dose-normalized AUC (ng*h/mL/mg)	2.6 (170)	3.6 (167)	1.76
Dose-normalized C_{max} (ng/mL/mg)	0.23 (182)	0.29 (149)	1.23
Steady-state (C2D1) ^b			
	No CYP3A inhibitor (n=12)	Strong CYP3A-inhibiting azole (n=81)	GMR
AUC (ng*h/mL)	4915 (56)	12042 (51)	2.45
C_{max} (ng/mL)	262 (52)	571 (46)	2.18

Data presented as geometric mean (geo % CV)
^a C1D1 NCA parameters in patients at all ziftomenib dose levels not receiving PPIs, ^b C2D1 PopPK parameters at the 600 mg QD dose level in patients not receiving PPIs
 GMR, geometric mean ratio

Source: Reviewer analysis.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Efficacy: In E-R analyses for efficacy, there was no significant relationship between ziftomenib exposure and response, suggesting that lower ziftomenib exposure in patients not receiving CYP3A-inhibiting azoles may not adversely impact efficacy [Section 14.4.3]. However, this assessment is limited by the limited sample size at dose levels other than 600 mg, the low CR + CRh rate overall, and the low proportion of patients who were not on CYP3A-inhibiting azoles.

Therefore, the FDA evaluated the effect of duration of strong CYP3A-inhibiting azole use on response in *NPM1-m R/R AML* (n=112, Phase 1b EAS + Phase 2). Patients were classified based on if they received strong CYP3A-inhibiting azoles for none (0%), some (1-75%), or the majority (over 75%) of study time (FDA Table 24).

There was no clear relationship between extent of strong CYP3A-inhibiting azole use and CR/CRh. Efficacy was generally comparable between patients receiving strong CYP3A-inhibiting azoles for 0% and greater than 75% of study time. Of note, decreased efficacy observed in the patients receiving strong CYP3A-inhibiting azoles for > 75% of study time when comparing to 1-75% of study time may be confounded by potentially worse overall status of patients requiring azole antifungals for the majority of study time.

This analysis further supports that lower ziftomenib exposure in patients not receiving CYP3A-inhibiting azoles may not adversely impact efficacy, and that these patients should receive the 600 mg dose.

FDA Table 24. Impact of Time on Strong CYP3A-inhibiting Azole on CR/CRh

	% of study time on strong CYP3A-inhibiting azole		
	0% (n=16)	1-75% (n=31)	> 75% (n=65)
CR	2 (12.5)	8 (26)	10 (15)
CRh	0	2 (6.5)	2 (3.1)
CR + CRh	2 (12.5)	10 (32)	12 (18)

Source: Reviewer analysis.

Safety: In E-R analyses for safety, there was no significant relationship between ziftomenib exposure and safety, suggesting that higher ziftomenib exposure in patients receiving CYP3A-inhibiting azoles may not adversely impact safety [Section 14.4.3]. However, this assessment is limited by the limited sample size at dose levels other than 600 mg and the low proportion of patients who were not on CYP3A-inhibiting azoles. Additionally, a concentration-dependent increase in QTc was observed in n=133 R/R AML patients receiving ziftomenib 600 mg QD, with the largest mean increase predicted to be 7.7 ms and 8% of patients with QTc over 500 ms and increase greater than 60 ms from baseline.

Therefore, the FDA evaluated the effect of duration of strong CYP3A-inhibiting azole use on safety in *NPM1-m R/R AML* (n=112, Phase 1b EAS + Phase 2) (FDA Table 25). There was no clear relationship between the extent of strong CYP3A-inhibiting azole use and incidence of

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TEAE, grade ≥ 3 TEAE, grade 5 TEAE, dose reduction, discontinuation, or grade ≥ 3 differentiation syndrome. However, there were increased incidences of SAE, dose interruption, all-grade differentiation syndrome, and all-grade and grade ≥ 3 febrile neutropenia in patients who received strong CYP3A-inhibiting azoles. Of note, these increased safety outcomes observed in the patients receiving strong CYP3A-inhibiting azoles for greater than 75% of study time (vs 0% of study time) may be confounded by worse overall status of patients requiring azole antifungals for the majority of study time. Additionally, ziftomenib exhibits concentration-dependent increases in QTc interval, for which risk may increase with coadministration of strong CYP3A inhibitors.

FDA Table 25. Impact of Time on Strong CYP3A-inhibiting Azole on Safety Outcomes

	% of study time on strong CYP3A-inhibiting azole		
	0% (n=16)	1-75% (n=31)	> 75% (n=65)
TEAE	16 (100)	31 (100)	65 (100)
Grade ≥ 3 TEAE	16 (100)	30 (97)	59 (91)
Grade 5 TEAE	5 (31)	6 (16)	17 (26)
SAE	11 (69)	57 (81)	53 (82)
Dose reduction	1 (6.3)	0	3 (4.6)
Dose interruption	6 (38)	21 (68)	33 (51)
Discontinuation	6 (38)	5 (16)	13 (20)
Differentiation syndrome	2 (12.5)	9 (29)	16 (25)
Grade ≥ 3 differentiation syndrome	2 (12.5)	7 (23)	6 (9.2)
Febrile neutropenia	2 (12.5)	6 (19)	17 (26)
Grade ≥ 3 febrile neutropenia	2 (12.5)	6 (19)	17 (26)

Source: Reviewer analysis.

Given the available PK, efficacy, and safety data, the FDA generally agrees that dose modifications in patients receiving strong or moderate CYP3A inhibitors appears reasonable. However, given that there may be increased risk of SAEs, dose interruption, differentiation syndrome, and QT prolongation in patients receiving strong CYP3A inhibitors, additional safety monitoring is warranted in these patients.

Additionally, a PMR will be issued to request the Applicant to complete the ongoing Study KOMEN-001 Sub-study 2 which evaluates the impact of itraconazole (strong CYP3A and P-gp inhibitor) on ziftomenib PK (FDA Table 22).

CYP3A Inducers: The FDA generally agrees with the Applicant's position that concomitant use of strong and moderate CYP3A inducers should be avoided, as coadministration is expected to decrease ziftomenib exposure by up to ~50% to 80% [Section 14.4.4].

CYP3A Substrates: The FDA generally agrees with the Applicant's assessment that ziftomenib has weak CYP3A inhibition potential when administered alone [Section 14.4.4].

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The Applicant has an ongoing KO-MEN-001 Sub-study evaluating the effect of ziftomenib on PK of midazolam (CYP3A substrate), for which a PMR will be issued to complete (FDA Table 22). However, coadministration of moderate CYP3A inhibitors (i.e., azoles) are permitted in the study, which are expected to have significant impact on midazolam PK, so data analysis may be complicated by confounding DDIs.

CYP1A2 Inhibitors: The FDA agrees with the Applicant's position that no dose adjustment is required when used concomitantly with CYP1A2 inhibitors.

Although ziftomenib was also metabolized by CYP1A2 *in vitro*, furafylline (CYP1A2 inhibitor) did not significantly reduce ziftomenib metabolism in human liver microsomes (HLMs), suggesting that CYP1A2 does not play a major role in ziftomenib disposition.

CYP2D6 Inhibitors: The FDA agrees with the Applicant's position that no dose adjustment is required when used concomitantly with CYP2D6 inhibitors.

Although ziftomenib was also metabolized by CYP2D6 *in vitro*, quinidine (CYP2D6 inhibitor) did not significantly reduce ziftomenib metabolism in HLMs, suggesting that CYP2D6 does not play a major role in ziftomenib disposition.

Transporter DDIs

P-gp Inhibitors: The FDA generally agrees with the Applicant's position that no dosage adjustment is needed when used concomitantly with P-gp inhibitors.

The Applicant's PopPK analysis indicated that concomitant use with P-gp inhibitors on the same day of ziftomenib administration has no clinically significant effect on ziftomenib PK [Section 19.4.2.2]. However, this analysis may be limited, as dosing time of P-gp inhibitor to ziftomenib is not recorded and there is the potential for overlapping substrate specificity, as many P-gp inhibitors are also CYP3A inhibitors. Additionally, the majority of patients received concurrent posaconazole, which is a strong CYP3A and P-gp inhibitor, and no dose adjustment is recommended with concurrent posaconazole based on clinical efficacy and safety data.

BCRP Inhibitors: The Applicant did not submit an assessment to evaluate the impact of BCRP inhibitors on ziftomenib PK. A PMR will be issued to this conduct this assessment (FDA Table 22).

ARAs

The FDA conducted an analysis to evaluate the potential patient-centric impact of ARA usage. Initially, there was not restriction on ARA use in KO-MEN-001. Following Protocol Version 6 (05/12/2022), use of PPI was prohibited, and staggered dosing of H2RAs (10 hours before or 2 hours after KOMZIFTI administration) was recommended. The FDA evaluated the distribution of PPI and H2RA use in the KO-MEN-001 mITT population, as shown in FDA Figure 4. The

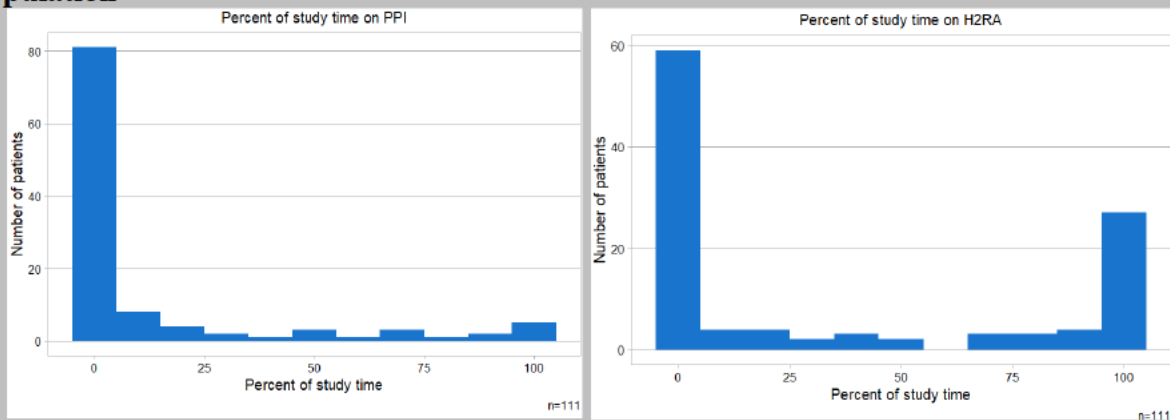
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majority of patients received PPIs for 0 to 10% of study time, given that approximately 90% of mITT population were enrolled after implementation of Protocol Version 6. In contrast, H2RA use was significantly more common, with nearly one-quarter of patients receiving H2RAs for 90 to 100% of study time, indicating the significant overall usage of ARAs.

FDA Figure 4. Percent of Study Time on PPI (left) or H2RA (right) in KO-MEN-001 mITT Population



Source: Reviewer analysis.

PPIs: The FDA

(b) (4)

recommends that concomitant use of PPIs be avoided.

The FDA agrees with the Applicant's assessment that concomitant use of PPIs decreases exposure by up to 70% (C_{max} =123 ng/mL [53%] vs 37 ng/mL [196%]; AUC_{inf} =2,490 ng*h/mL [58%] vs 1,170 ng*h/mL [95%]). Additionally, the FDA assessed the effect of PPIs on ziftomenib PK at C1D1, as shown in

FDA Table 26. Patients were stratified by azole antifungal use, given that ziftomenib exposure increases when ziftomenib is coadministered with strong CYP3A inhibitors. There was a limited sample size and high variability in ziftomenib PK, resulting in wide 90% CIs. However, the result of the FDA analysis was consistent with those of the dedicated DDI study with rabeprazole.

(b) (4)

. However, the FDA does not agree with the conclusions of the PBPK model, as the simulated gastric pH at the proposed administration times are mostly above the pH at which the DDI was clinically observed [Section 14.4.4]. Therefore, the FDA recommends prohibiting concomitant PPI use.

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FDA Table 26. Ziftomenib PK Parameters with PPI and H2RA Inhibitor Use

	Dose-normalized C _{max}		Dose-normalized AUC _{last}		Dose-normalized AUC ₀₋₂₄	
	ng/mL/mg	GMR	ng*h/mL/mg	GMR	ng*h/mL/mg	GMR
Any azole						
No ARA (n=13)	0.23 (179.7)	-	2.2 (191.6)	-	2.6 (159.9)	-
Antacid (n=3)	0.34 (209.9)	1.48 (0.45, 4.86)	2.8 (207.5)	1.23 (0.37, 4.11)	2.7 (203.7)	1.04 (0.31, 3.42)
H2RA (n=7)	0.35 (98.9)	1.53 (0.64, 3.65)	3.8 (142.7)	1.71 (0.71, 4.14)	4.2 (156.0)	1.60 (0.63, 4.03)
PPI (n=16)	0.07 (150.2)	0.30 (0.15, 0.59)	0.8 (129.8)	0.34 (0.17, 0.69)	0.8 (136.9)	0.29 (0.14, 0.60)
Strong azoles						
No ARA (n=5)	0.23 (260.7)	-	2.9 (210.0)	-	2.9 (210.9)	-
H2RA (n=6)	0.35 (112.2)	1.56 (0.45, 5.39)	4.0 (164.8)	1.37 (0.42, 4.48)	4.5 (186.2)	1.56 (0.42, 5.76)
PPI (n=8)	0.10 (172.6)	0.44 (0.14, 1.42)	1.1 (129.2)	0.39 (0.13, 1.19)	1.2 (139.4)	0.43 (0.13, 1.43)

Parameters presented as geometric mean (geometric % CV); GMR presented as GMR (90% CI)

Source: Reviewer analysis.

H2RAs: The FDA generally agrees with the Applicant’s position that H2RAs can be concomitantly used but that staggered dosing of H2RAs is appropriate (10 hours before or 2 hours after KOMZIFTI administration).

The Applicant’s PopPK analysis indicated that concomitant use with H2RA inhibitors on the same day of ziftomenib administration has no clinically significant effect on ziftomenib PK [Section 19.4.2.2]. However, this analysis may be limited, as dosing time of H2RA inhibitor to ziftomenib is not recorded, and approximately 50% of patients were treated when there was not restriction on ARA use in KO-MEN-001. Therefore, the FDA assessed the effect of H2RAs on ziftomenib PK at C1D1, as shown in

FDA Table 26. Patients were stratified by azole antifungal use, given that ziftomenib exposure increases when ziftomenib is coadministered with strong CYP3A inhibitors. There was a limited sample size and high variability in ziftomenib PK, resulting in wide 90% CIs. However, the analysis demonstrated that there is no evidence that coadministration of ziftomenib with H2RAs decreases ziftomenib PK (GMRs ranged from 1.37 to 1.71).

Additionally, the FDA evaluated the effect of duration of H2RA use on response in *NPM1*-m R/R AML (n=112, Phase 1b EAS + Phase 2; FDA Table 27). Patients were classified based on if they received strong CYP3A-inhibiting azoles for minimum (1 - 10%), some (11-75%), or the majority (more than 75%) of study time.

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There was no clear relationship between extent of H2RA use and CR + CRh. Efficacy of ziftomenib in patients receiving H2RA at least 75% of study time appeared comparable to patients receiving H2RA at 0-10% of study time. Therefore, a staggered dosing of H2RAs (10 hours before or 2 hours after KOMZIFTI administration) appears reasonable, which is also consistent with ziftomenib dosing guidance with regard to H2RA during KO-MEN-001 (as of Protocol Version 6 [05/12/2022]).

FDA Table 27. Impact of Time on H2RA on CR/CRh

	% of study time on H2RA		
	0-10% (n=61)	11-75% (n=17)	> 75% (n=34)
CR	11 (18)	4 (24)	5 (15)
CRh	4 (7)	1 (6)	2 (6)
CR + CRh	15 (25)	5 (29)	7 (21)

Source: Reviewer analysis.

Antacids: The FDA does not agree with the Applicant's position that administration of locally-acting antacids ^{(b) (4)}

The FDA is recommending that administration of locally-acting antacids be staggered 2 hours before or 2 hours after ziftomenib administration.

There was no dedicated DDI study evaluating the impact of coadministration of ziftomenib with locally-acting antacids on ziftomenib PK. However, given that coadministration of ziftomenib with PPIs decreases ziftomenib exposure by ~60 to 70%, it is reasonable to stagger ziftomenib dosing with locally-acting antacids. Staggering by 2 hours before or 2 hours after ziftomenib administration may be reasonable given the short duration of action for antacids.

Additional DDIs

QTc-prolonging drugs: The FDA does not agree that ziftomenib does not have clinically meaningful impact on QTc prolongation, and therefore PD-mediated DDIs with other QTc-prolonging drugs may occur. The FDA recommends that concomitant use of QTc-prolonging drugs should be avoided. If concomitant use cannot be avoided, additional safety monitoring is recommended. Interrupt administration if QTc interval is over 500 ms or change from baseline is over 60 ms.

Patients receiving ziftomenib 600 mg displayed a concentration-dependent increase in QTc interval (largest mean increase in QTc predicted to be 7.7 ms), with 8% of patients experiencing QTcF over 500 ms and QTc increase over 60 ms over baseline.

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

An overview of clinical studies supporting the efficacy and safety of ziftomenib is presented in [Applicant Table 3](#). The healthy volunteer studies are not included.

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Applicant Table 3: Applicant - Clinical Studies Supporting the Efficacy and Safety of Ziftomenib

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Studies to Support Efficacy and Safety</i>								
KO-MEN-001 Pivotal main study	NCT 04067336	Phase 1/2, open-label, multicenter safety and efficacy study	Ziftomenib: Phase 1: Part 1a, Cohorts 1 to 7: 1: 50 mg QD PO (n=1)2: 100 mg QD PO (n=1) 3: 200 mg QD PO (n=6) 4: 400 mg QD PO (n=5) 5: 600 mg QD PO (n=5) 6: 800 mg QD PO (n=11) 7: 1000 mg QD PO (n=1) Part 1b, Cohorts 1 and 2 1: 200 mg QD PO (n=17) 2: 600 mg QD PO (n=36) Phase 2: 600 mg QD PO (n=92)	Primary: Phase 1a: determine MTD and/or RP2D of ziftomenib in patients with R/R AML. Phase 1b: determine the safety, tolerability, and MBED of ziftomenib in biomarker-specific dosing cohorts. Phase 2: assess CR/CRh rate	Treatment continued until disease progression, no longer receiving clinical benefit, or drug intolerance	As of DCO: 175 On treatment: 9 On study: 28	Patients with R/R AML	52 centers: 23 centers in the US 29 centers in Belgium, Canada, France, Germany, Italy, Spain, and the United Kingdom
<i>Studies to Support Safety Only</i>								
KO-MEN-001 Substudy 1 (supportive)	NCT 04067336	Phase 1, multicenter, open-label, safety and drug-drug interaction	Ziftomenib: 600 mg QD PO, 28-day cycles Midazolam: 2 mg PO single dose, on Cycle 1 Day 1 and a	Primary: PK parameters of midazolam and 1-hydroxymidazolam: AUC0-24h, AUC0-t,	Treatment continued until disease progression, no longer receiving clinical	As of DCO: 7	Patients with R/R AML with mutations associated with MEIS1 overexpression in absence of	6 centers in the US

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		(CYP3A4 inducer)	single dose on Cycle 1 Day 15	Cmax, Tmax, t1/2, CL/F, and Vz/F PK parameters of ziftomenib and ziftomenib metabolites: AUC0-24h, AUC0-t, Cmax, Tmax, t1/2, CL/F, and Vz/F	benefit, or drug intolerance		<i>NPM1</i> -m or <i>KMT2A</i> -r	
KO-MEN-001 Substudy 2 (supportive)	NCT 04067336	Phase 1, multicenter, open-label, safety and drug-drug interaction (CYP3A4 inhibitor)	Ziftomenib: 600 mg QD PO, 28-day cycles Itraconazole: 200 mg BID PO, Cycle 1 Days 19 to 25	Primary: PK parameters of ziftomenib and ziftomenib metabolites: AUC0-∞, AUC0-t, Cmax, Tmax, t1/2, CL/F, and Vz/F PK parameters of itraconazole: AUC0-∞, AUC0-t, Cmax, Tmax, t1/2, CL/F, and Vz/F	Treatment continued until disease progression, no longer receiving clinical benefit, or drug intolerance	As of DCO: 4	Patients with R/R AML with mutations associated with MEIS1 overexpression in absence of <i>NPM1</i> -m or <i>KMT2A</i> -r	8 centers in the US
KO-MEN-001 Substudy 3 (supportive)	NCT 04067336	Phase 1, multicenter, open-label, safety and efficacy	Ziftomenib: 200 mg, 400 mg, 600 mg QD (100 mg QD optional) PO	Primary: determine the safety, tolerability, and MBED/RP2D	Treatment continued until disease progression, no longer receiving clinical benefit, or	As of DCO: 5	Patients with R/R <i>KMT2A</i> -r ALL	35 centers 16 centers in the US, 19 centers in the EU

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					drug intolerance			
KO-MEN-007 (supportive)	NCT 05735184	Phase 1, multicenter, open-label, safety, tolerability, PK, efficacy of ziftomenib combined with standard-of-care treatments	Ziftomenib: 200 mg, 400 mg, and 600 mg QD PO on Cycle 1 Day 8 and continuously thereafter Venetoclax/azacitidine: Target dose of venetoclax 400 mg QD PO on Days 1 to 28 (with 3-day ramp up beginning with 100 mg on Cycle 1 Day 1) and azacitidine 75 mg/m²/day SC or IV on Days 1 to 7 of 28-day cycle Daunorubicin/cytarabine (7+3) induction: cytarabine 100-200 mg/m²/day IV on Days 1 to 7 with daunorubicin 60 mg/m²/day IV on Days 1 to 3 of induction cycle 1, Days 1-2 if 2nd remission induction cycle req'd. Consolidation: intermediate-dose cytarabine 1500 mg/m²/day or high-dose cytarabine 3000	Primary: 1) determine the safety and tolerability of ziftomenib combined with standard of care treatments in adults with newly diagnosed and R/R <i>NPM1</i>-m or <i>KMT2A</i>-r AML 2) determine the clinical activity of ziftomenib combined with standard of care treatments.	Treatment continued until disease progression, no longer receiving clinical benefit, or drug intolerance	As of DCO: 146	Patients with 1L or R/R <i>NPM1</i> -m or <i>KMT2A</i> -r	37 centers in the US

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			mg/m2/day on Days 1, 3, and 5 of Cycle 1-4. VYXEOS™ induction: VYXEOS™ (daunorubicin 44 mg/m2 and cytarabine 100 mg/m2) IV infusion over 90 minutes on Days 1, 3, and 5 of induction Cycle 1 and on Days 1 and 3 for induction Cycle 2, if needed					
KO-MEN-008 (supportive)	NCT 06001788	Phase 1, multicenter, open-label, safety, tolerability, PK and efficacy of ziftomenib combined with standard-of-care treatments	Ziftomenib: In combination with FLAG-IDA/LDAC: 200 mg, 400 mg, and 600 mg QD (100 mg QD optional) on Cycle 1 Day 8 and continuously thereafter In combination with gilteritinib: 100 mg, 200 mg, 400 mg, 600 mg QD (50 mg QD optional) FLAG-IDA: fludarabine 30 mg/m2/day IV on Days 1 to 4, idarubicin 6 to 10 mg/m2/day IV on Days 1 to 3, cytarabine 1500 to 2000 mg/m2/day	Primary: 1) determine the safety and tolerability of ziftomenib combined with standard of care treatments in adults with newly diagnosed and R/R <i>NPM1</i>-m or <i>KMT2A</i>-r AML 2) determine the clinical activity of ziftomenib combined with standard of care treatments.	Treatment continued until disease progression, no longer receiving clinical benefit, or drug intolerance	As of DCO: 22	Patients with newly diagnosed high-risk, newly diagnosed, and R/R <i>NPM1</i> -m or <i>KMT2A</i> -r AML	25 centers: 19 centers in the US 6 centers in Italy and Spain

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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			IV on Days 1 to 4, and G-CSF 300 µg/m ² /day SC on Days -1 to 5					

Note: Table does not include the healthy volunteer studies (KO-MEN-003, KO-MEN-005, KO-MEN-006) or KO-MEN-001 Substudy 4 which was not active and had not enrolled any patients at the time of the data cutoff.

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The Applicant's Position:

The primary evidence of efficacy and safety for ziftomenib in adult patients with R/R AML with *NPM1* mutations is based on the ongoing Phase 1/2 study, KO-MEN-001. The primary analysis of the Phase 2 cohort (N=92) with a data cutoff date of 28 OCT 2024 serves as the primary basis of efficacy for the proposed indication. The study is supported by confirmatory evidence from the Phase 1b portion of KO-MEN-001 which enrolled 20 R/R *NPM1*-m AML patients treated at the proposed dose of 600 mg QD. The primary safety population supporting the proposed indication is based on the total of 112 patients across these 2 studies.

Supportive safety information is derived from other ongoing clinical studies of ziftomenib. The KO-MEN-001 sub-studies are evaluating drug-drug interactions in non-*NPM1*-m AML (sub-studies 1 and 2) or ziftomenib activity in acute lymphoblastic leukemia (sub-study 3), and Studies KO-MEN-007 and KO-MEN-008 evaluate ziftomenib in combination with standard-of-care regimens (eg, venetoclax, azacitidine, intensive and low-dose chemotherapy, and gilteritinib). As these data do not directly inform the proposed indication of patients with R/R *NPM1*-m AML due to the inherent heterogeneity of combination agents, molecular types and study populations, summary-level data are presented in the application for a comprehensive package.

The clinical studies supporting the efficacy and safety of ziftomenib are summarized above and have been included in the submission.

The FDA's Assessment:

The FDA agrees with the Applicant's description of their Clinical Studies relevant to this Application. The FDA review was primarily based on data from NDA 220305, relevant published literature, and relevant information in the public domain.

Study KO-MEN-001 is the pivotal study that was the basis for establishing the safety and efficacy of ziftomenib in patients with R/R *NPM1*-m AML. The Applicant submitted a complete dataset for this study, using a data cut date of 10/28/2024, at the time of the initial NDA submission (03/31/2025). This data set forms the basis for most of this clinical review. Updated efficacy and safety using a data cut of 03/21/2025 were also utilized as part of the safety update.

7.2. Review Strategy

The FDA's Assessment:

At the time of the NDA submission, the Applicant submitted datasets from 5 additional studies in patients with AML and 4 studies in healthy volunteers. Data from the additional studies were used to supplement the analysis of safety.

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The Applicant submitted an updated data set for Study KO-MEN-001, using a data cut date of 3/21/2025, at the time of the 90-day safety update (SN0015; submitted to eCTD on 06/27/2025) that included updated efficacy data for those patients that remained on treatment at the time of the original data cut date. This updated efficacy data cut was used for the final efficacy analysis. FDA considered the pooled population of patients with R/R AML with an *NPM1*-m treated at the recommended dose of 600 mg QD as the efficacy and safety population for consideration. This included a total of 112 patients (20 patients from the phase 1b cohort and 92 patients from the phase 2 cohort). Patients were pooled to provide a consistent and relevant population for both the safety and efficacy analyses. The FDA considered this to be reasonable as the inclusion criteria for patients in the Phase 1b and Phase 2 cohorts were identical, and these were single-arm cohorts being pooled a single group, allowing for the best estimate of the efficacy and safety in this population.

Summaries of data and statistical analyses by the reviewer were performed using JMP 17.0 (SAS Institute, Inc. Cary, NC), R Statistical Software (version 4.3.1; R Core Team 2020), and SAS 9.4 (SAS Institute, Inc. Cary, NC). MedDRA Adverse Events Diagnostic Version 4.5.1 (MAED) (FDA, Silver Spring, MD) and OncoSET (FDA, Silver Spring, MD) were used to look for safety signals.

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8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. KO-MEN-001

Trial Design

The Applicant's Description:

Basic Study Design

KO-MEN-001 is an ongoing Phase 1/2, first-in-human, open-label, multiple cohort study of the menin inhibitor, ziftomenib, in adult patients with R/R AML. A graphical representation of the study is provided in Applicant Figure 1.

The Phase 1 portion consisted of 2 parts: dose-escalation (Part 1a) and dose-validation/expansion (Part 1b). In the Part 1a portion of the study, 30 R/R AML patients received ziftomenib in doses ranging from 50 to 1000 mg QD and an MTD of 800 mg daily was established. Based on safety, tolerability, PK, and preliminary antileukemic activity observed in Part 1a, Part 1b was initiated for expansion at 2 dose levels (200 mg and 600 mg QD) in a total of 53 patients with *KMT2A-r* or *NPM1-m* AML, to determine the RP2D. Based on the totality of efficacy, safety, and PK data after completing Phase 1, the RP2D of ziftomenib was determined to be 600 mg QD for adult patients with R/R *NPM1-m* AML administered in continuous 28-day cycles.

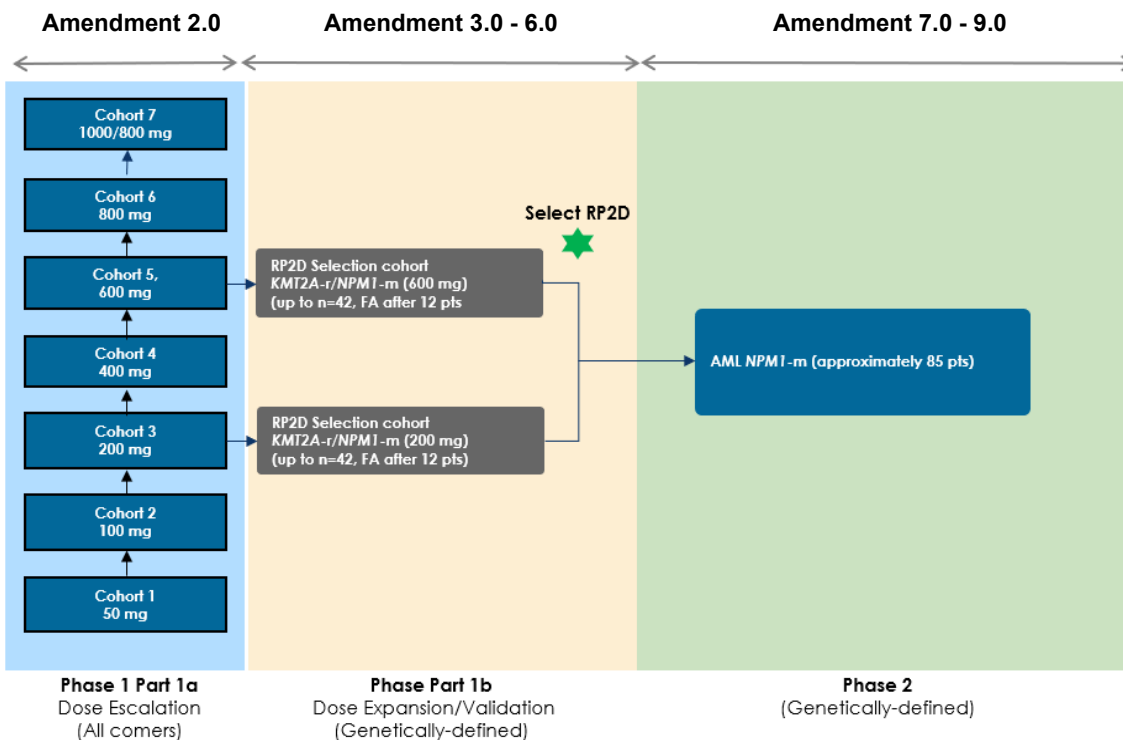
The Phase 2 portion of KO-MEN-001 was a single-cohort study evaluating ziftomenib 600 mg QD in patients with locally determined R/R *NPM1-m* AML. The Phase 2 study is the primary basis of efficacy for this application; the primary analysis was performed when the planned sample size of 85 patients had been followed for at least 6 cycles or discontinued earlier, as prespecified in the study protocol and statistical analysis plan. Patients could continue treatment with ziftomenib until disease progression or unacceptable toxicity, and patients were permitted to resume treatment with ziftomenib following hematopoietic stem cell transplant (HSCT).

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Applicant Figure 1: Applicant - KO-MEN-001 Phase 1 and 2 Study Design



Abbreviations: AML=acute myeloid leukemia; CSR=clinical study report; FA=full analysis; *KMT2A-r*=lysine[K]-specific methyltransferase 2 rearranged; *NPM1-m*=nucleophosmin-mutant; RP2D=recommended Phase 2 dose.

Note: approximate numbers of planned patients are presented.

Source: Figure 2 of the KO-MEN-001 CSR

Trial Location and Applicability of Foreign Data

The ziftomenib clinical development program was designed globally and encompassed studies conducted worldwide. The pivotal Phase 2 portion of Study KO-MEN-001 was conducted at 40 study centers in 7 countries including the US, Canada, Belgium, France, Germany, Italy, and Spain. The standards of care and treatment of patients with R/R *NPM1-m* AML are similar for patients located across all regions included in the clinical studies applicable to this NDA. Furthermore, ziftomenib PK analyses assessed race and ethnicity as intrinsic factors with no clinically relevant findings based on these variables. In accordance with 21 CFR 312.120, Good Clinical Practice, compliance statements are provided for sites participating in the studies included in the ziftomenib development program to support the quality and integrity of the clinical study data from sites outside of the US as applicable to the assessment of the safety and

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efficacy of ziftomenib for the proposed indication for this NDA. Overall, no issues were identified with respect to the applicability of foreign data to the US population.

Administrative Structure

A data monitoring committee (DMC) monitored emerging data throughout Phase 1 and an independent DMC was established for Phase 2 to periodically review emerging safety data to identify if any safety or other concerns arise that may have affected patient or study continuation, per the charter.

Study Treatment

Ziftomenib capsules were orally administered in continuous 28-day cycles at a dosage of 600 mg once daily (QD). Ziftomenib was administered in the fasted state (1 hour before or 2 hours after a meal). No dose adjustments were required for concomitant administration of CYP3A4 inhibitors.

Study Assessments

The Phase 2 Schedule of Assessments is provided in the KO-MEN-001 Protocol, Table 4. Key efficacy and safety assessments included:

- Blood, bone marrow aspirate or biopsy collection for response assessment on the last day of each cycle (± 5 days). Once clearance was documented, BM sampling could occur every 3 months thereafter.
- Blood sampling for hematology, chemistry, and coagulation safety assessment at screening; Cycle 1 Day 1, Day 4, Day 8, Day 10, Day 15; and Day 1 of every cycle thereafter.
- Triplicate 12-lead ECGs at screening; Cycle 1 Day 1, Day 8, Day 15; and Day 1 of every cycle thereafter.
- Directed physical examination and vital signs at each study visit.

The FDA's Assessment:

The FDA generally agrees with the description of KO-MEN-001. Although the study design allowed patients to resume treatment with ziftomenib following HSCT, the study protocol only required minimum conditions for post-HSCT eligibility, such as minimal count recovery (ANC $\geq 0.5 \times 10^9/L$ and platelets $\geq 20 \times 10^9/L$), non-hematologic transplant AEs $<$ grade 2, no active GVHD, a maximum of 0.5 mg/kg of prednisone equivalent, and stable doses of calcineurin inhibitors. The study was neither designed nor conducted to evaluate the benefit and risk profile of such post HSCT resumption.

The bone marrow aspirate or biopsy samples were collected monthly before the patients achieved at least MLFS, every three months thereafter, and as needed if there were signs of relapse. CBCs were conducted at least weekly until patients achieved clearance of leukemia in the bone marrow and then at least monthly thereafter. Since bone marrow sampling would switch

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to every three months based on clearance of blasts irrespective of peripheral count recovery, the window between bone marrow showing blast clearance (< 5% blasts) and the CBC showing blood count recovery might be as long as one month or even longer. This was reflected in the investigators' reported responses in the submitted datasets. The FDA adjudicated all the responses with a two-step approach based on the schedule of assessments and clinical judgement. First, FDA applied a window of -7 days to +14 days for peripheral count recovery around the bone marrow assessment dates. If the marrow was in morphologic remission and the peripheral counts made the criteria for CR or CRh in this window, the FDA agreed on a time of response of the marrow sampling. Second, if the marrow showed blast response without the peripheral counts meeting criteria for CR or CRh in the -7 to +14 day window but later meeting criteria for CR or CRh after day 14, the FDA would consider it a response if the marrow was still in remission at the next bone marrow assessment. The FDA posited that demonstration of bone marrow remission before and after count recovery could be extrapolated to reasonably assume that the marrow was in remission at the time of count recovery, had it been assessed on that day. For these cases, the FDA would assign the time of remission as the time of peripheral count recovery.

Eligibility Criteria

The Applicant's Description:

The Phase 2 portion of KO-MEN-001 (N=92) was conducted in adult patients with R/R *NPM1*-m AML who received 600 mg QD in line with the proposed indication population. The eligibility criteria for the Phase 2 portion of KO-MEN-001 were appropriate for and reflective of the patient population for the proposed indication. The key inclusion criteria for KO-MEN-001 were as follows:

- R/R AML defined as those who have also failed or are not appropriate for any approved SOC therapies, or HSCT with reappearance of $\geq 5\%$ blasts in the BM. In addition, patients must have at least one of the following genomic alterations:
 - Phase 1b: Adult R/R AML patients that have a documented KMT2A-r or,
 - Phase 1b and Phase 2: Adult R/R AML patients that have a documented NPM1-m.
- ≥ 18 years of age
- Adequate organ function including:
 - Creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation
 - Serum bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN) (unless known Gilbert's syndrome or secondary to leukemic disease)
 - AST and ALT $\leq 2.0 \times$ ULN
- Peripheral WBC counts $\leq 30,000/\mu\text{L}$.
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 , and a life expectancy of at least 2 months

The key exclusion criteria were as follows:

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- Diagnosis of acute promyelocytic leukemia or chronic myelogenous leukemia in blast crisis.
- Donor lymphocyte infusion < 30 days prior to study entry.
- Clinically active central nervous system (CNS) leukemia.
- Has undergone HSCT and has not had adequate hematologic recovery.
- Patients on immunosuppressive therapy post HSCT must be off all immunosuppression therapy within 2 weeks of Cycle 1 Day 1
- $\geq$ Grade 2 active acute GvHD, moderate or severe limited chronic GvHD, or extensive chronic GvHD of any severity.
- QTcF > 480 msec
- Has received prior menin inhibitor

The FDA's Assessment:

FDA agrees with the Applicant's description of the eligibility criteria. The FDA also notes that eligible *NPM1* mutations included Type A, B, and D mutations caused by 4-base nucleotide insertions in exon 11 and other *NPM1* mutations that were likely to result in cytoplasmic localization of the *NPM1* protein.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint for Phase 2 was the CR/CRh rate. CR/CRh rate is an accepted binary efficacy endpoint commonly used to demonstrate direct clinical benefit to support full approval of treatments for AML in the palliative setting, per FDA guidance for industry (Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment; 2022). This approach, with demonstration of durability and transfusion independence, was used previously with FDA-approved targeted inhibitors in R/R acute leukemia (eg, revumenib, olutasidenib, ivosidenib, enasidenib, gilteritinib).

The response endpoints were defined in accordance with FDA guidance and 2022 ELN guidelines as shown in

Applicant **Table 4**. Secondary efficacy endpoints included duration of CR/CRh, transfusion independence, CR/CRh with MRD negativity, CRc (CR+CRh+CRi), ORR (CR+CRh+CRi+MLFS+PR), EFS, and OS. Data from these endpoints are presented as additional evidence of clinical benefit in support of the primary endpoint. The Phase 1b portion

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of the study, which provides supporting confirmatory evidence and is included in Section 8.1.2, used the same efficacy endpoints.

Applicant Table 4: Applicant - Response Criteria Definitions

Response Criteria	BM Blasts (%)	Neutrophils (μL)	Platelets (μL)	Peripheral Blasts	Other
Complete Remission (CR)	< 5	≥ 1,000	≥ 100,000	Absence of circulating blasts	No EMD
Complete Remission with partial hematologic recovery (CRh)	< 5	≥ 500	≥ 50,000	Absence of circulating blasts	No EMD
Complete Remission with incomplete hematologic recovery (CRi)	< 5	< 1,000	< 100,000	Absence of circulating blasts	No EMD
Morphologic leukemia-free state (MLFS)	< 5	N/A	N/A	Absence of circulating blasts	No EMD; BM should not be merely aplastic; BM spicules should be present; at least 200 cells in the aspirate or cellularity at least 10% in the biopsy
Partial Remission (PR)	Decreased pretreatment BM blast by 50%; decreased BM blast percentage to 5 to 25%	≥ 1,000	≥ 100,000	Absence of circulating blasts	N/A

Source: KO-MEN-001 Protocol Section 9.6.1, Table 16

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The FDA's Assessment:

The FDA adjudicated the CR + CRh responses using slightly different definitions than described in

Applicant **Table 4**: the FDA used $>$ rather than $\geq$ for the thresholds for blood recovery counts. As such, counts were required to be: neutrophil count $> 1,000 \mu\text{L}$ and platelet count $> 100,000 \mu\text{L}$ for CR and neutrophils $> 500 \mu\text{L}$ and platelets $> 50,000 \mu\text{L}$ for CRh. The difference in the treated patients' response type and date between the investigator's assessments and the FDA's adjudication is summarized below in Data Quality and Integrity section.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The SAP incorporated Agency feedback and the one amendment of the SAP, version 2, was finalized prior to the database lock for the planned primary analysis.

The SAP defined the following analysis populations for primary efficacy and safety evaluation:

Modified Intent-to-Treat (mITT): all patients who received at least 1 dose of ziftomenib. The Phase 2 mITT was used for the primary efficacy and safety analysis.

Efficacy Analysis Set (EAS): all patients with locally confirmed *NPM1* mutations who received an initial dose of 600 mg QD ziftomenib. A supportive efficacy analysis was conducted using the Pooled Population, which includes the Phase 1 Part 1b EAS and Phase 2 mITT analysis set.

Per-Protocol Analysis Set (PPS): all Phase 2 mITT patients who received at least 21 days of ziftomenib and had no significant protocol deviations that could substantially impact the results of the primary analysis. A supportive analysis using the PPS was performed for the evaluation of CR/CRh rate.

The primary efficacy endpoint was CR/CRh rate, a palliative endpoint routinely accepted in this treatment setting for targeted agents. The Phase 2 sample size of at least 85 patients was chosen to evaluate the safety profile further and secure adequate power to determine whether the CR/CRh rate of ziftomenib was greater than the null hypothesis of 0.12 (a CR/CRh rate of 12% based on overestimated historical data of R/R *NPM1*-m patients in a clinical trial control arm). With a 1-sided alpha of 0.025, a total of 85 *NPM1*-m patients provided 89% power to exclude the null hypothesis. The estimand for the primary endpoint analysis is detailed in the SAP Section 7.5.1.

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The primary analysis was triggered when 168 days had passed since the 85th *NPM1*-m patient was dosed or when the last patient had completed their safety follow-up period and/or End of Study. The timing of the primary analysis was set to ensure that at least 85 patients, the planned sample size, had a minimum of 168 days of follow-up time, which corresponded to the maximum number of treatment cycles (6 cycles) that could be completed in a 6-month period.

Key secondary endpoints to further support clinical benefit demonstrated by CR/CRh rate included duration of CR/CRh and transfusion independence. Duration of CR/CRh was defined, for patients who achieved BOR as CR or CRh, as the time from the first occurrence of CR or CRh to documented hematological relapse or death due to any cause, whichever occurs first. TI was defined as the absence of red blood cell (RBC) and platelet transfusions for at least 56 consecutive days in post-baseline period.

Restricted mean survival time (RMST) was added as a post-hoc analysis as an alternative approach to estimating DOR. The restricted mean survival time for duration of CR, duration of CRh, duration of CR/CRh, duration of CRc, and duration of ORR have been summarized using various truncation time points, including 9 months, 12 months, the time point when at least 10% of patients remained at risk, and the maximum observed duration.

No interim analysis was performed. An interim analysis was originally planned for Phase 2 but following Agency feedback regarding the size of the overall safety population, it was removed. The interim analysis was excluded from the SAP before the analysis timepoint and subsequently removed from the protocol in Amendment 9. All alpha was allocated to the primary analysis. Rules for the handling of missing data were specified in the SAP Section 5.2 to ensure overall data integrity.

Factors for planned subgroup analyses included sex, race, region, age, number of prior lines of therapy, prior HSCT, prior venetoclax exposure, subtypes of *NPM1* mutation, baseline ECOG performance score, baseline extramedullary disease status, and sub-type of AML. Subgroup analyses of baseline co-mutation status (eg, FLT3, IDH1/2) may also be performed.

The FDA's Assessment:

The Applicant justified the null rate of 12% based on the following related data and literature:

- The subgroup of patients with *NPM1*-m AML from the ADMIRAL study comparing gilteritinib versus investigator choice salvage chemotherapy in R/R AML. Although a significant proportion of patients in the *NPM1* mutated subgroup from the ADMIRAL study received high intensity chemotherapy, which would be inappropriate for KO-MEN-001 patients, the CR + CRh rate of the chemotherapy salvage therapy was 15.3% in patients either refractory to or relapsing following first-line induction therapy.⁷

⁷ Perl AE, et al (2019). Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *New Engl J Med*: 381: 1728-40.

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- The patients with first relapse or refractory AML from the VALOR study comparing vosaroxin + cytarabine vs. cytarabine salvage therapy. The CR rate of the cytarabine salvage therapy was 16.3%.⁸
- The CR response of patients treated in second salvage with a less intense therapy was only 4% regardless of the intensity of the first salvage therapy.⁹ In patients treated with venetoclax in combination with hypomethylating agents or low dose cytarabine where the majority of patients (84%) had received ≥ 2 prior therapies, the CR + CRi response was 12%.¹⁰
- Furthermore, despite the higher response rates observed in the R/R setting, patients with *NPM1*-m did not retain a favorable prognostic impact as compared to *NPM1*-wt, and the probability of achieving a response also declined with each sequential line of salvage therapy.¹¹

FDA noted the aforementioned literature sources did not include the same disease population as the proposed indication of R/R AML with *NPM1*-m; in particular, for multiple sources, the reported response rates were provided for the general population of patients with R/R AML rather than a specific subgroup of patients with *NPM1*-m. However, with the expectation that the *NPM1* mutation does not represent either a more favorable or unfavorable prognostic factor in the R/R disease space, these literature sources were considered for contextual purpose to understand the performance of low intensity chemotherapy in the proposed study population.

Regarding the primary endpoint of CR + CRh, FDA had the following considerations regarding its estimands for primary analysis:

- Analysis set: Phase 2 mITT per SAP. FDA used the pooled patient population from Phase 1 and 2 of adult patients who had R/R AML with an eligible *NPM1* mutation and who received at least one dose of 600 mg of ziftomenib as the primary analysis set to evaluate the effectiveness in the proposed disease population. This pooled analysis set is referred to as the Pooled Efficacy Cohort in this review.
 - The Phase 2 cohort and Phase 1b cohort were also evaluated separately, as per the SAP, and are included in the FDA's review.

⁸ Ravandi F, et al (2015). Vosaroxin plus cytarabine versus placebo plus cytarabine in patients with first relapsed or refractory acute myeloid leukaemia (VALOR): a randomized, controlled, double-blind, multinational, phase 3 study. *Lancet Oncol*: 16:1025-36.

⁹ Araki D, et al (2015). What qualifies as "true" salvage therapy in acute myeloid leukemia?: CR rates with second salvage depending on type of first salvage. *Clinical Lymphoma Myeloma and Leukemia*. 15:S191-2.

¹⁰ DiNardo CD, et al (2018). Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. *Am J Hematol*. 93:401-7.

¹¹ Venugopal S, et al (2021). *NPM1* mutations do not retain a favorable prognostic impact in adults with advanced relapsed or refractory (R/R) acute myeloid leukemia (AML). *Blood*. 138:S1:2287

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- Handling of intercurrent events was the same in SAP and this review for primary analysis:
 - Starting new anti-cancer therapy (including HSCT): while on treatment policy strategy, i.e., response is considered only up to the initiation of new therapy.
 - Discontinuation of treatment: treatment policy strategy, i.e., treatment discontinuation is ignored, and response data are continued to be followed up.
- Handling of missing data was the same in SAP and this review for primary analysis: patients with no post-baseline response assessment were assumed to have not achieved CR + CRh (composite strategy).
- The analysis method was the same in SAP and this review for primary analysis: Clopper-Pearson exact 95% CI, whose lower bound was compared against the benchmark of 12%.

Regarding DOR, the SAP specified the following censoring rules:

- Starting new anti-cancer therapy (including HSCT): censor at the last assessment date prior to the initiation of new therapy.
- Loss to follow up or withdrawal by patient: censor at the last assessment date prior to these intercurrent events.

A difference in the censoring rules of DOR with the above specifications is that the FDA considers HSCT as one standard of care for the study population and therefore would not censor at the date of receiving HSCT in the primary analysis of DOR.

Regarding the removal of the originally planned interim analysis, the Applicant communicated this to FDA on 12 January 2023 (IND 142028, SDN 164). However, this was not reflected in the protocol amendment 8 dated 11 May 2023, but was reflected later in SAP dated 20 September 2023 and protocol amendment 9 dated 13 September 2024. See Applicant Table 5 for more details.

Regarding the analysis of TI, the baseline period was not explicitly defined in the protocol nor the SAP. The primary analysis reported in CSR used the time window of 28 days prior to the first dose of study treatment to 28 days post the first dose or the last dose, whichever was earlier. FDA did not agree with this unconventional definition for the primary analysis and applied an alternative window for the primary analysis, which was 28 days prior to the first dose of study treatment to the first dose.

Protocol Amendments

The Applicant's Description:

As of the cutoff date for this NDA, there were nine KO-MEN-001 protocol amendments. Key changes are provided in [Applicant Table 5](#).

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Applicant Table 5: Applicant - Protocol Amendments to Study KO-MEN-001

Protocol version	Date	Key Changes
Original, Version 1.0	18 JAN 2019	Initial version
Version 2.0	04 MAR 2020	• Inclusion of KMT2A-r and NPM1-m AML patients in the dose escalation phase • Modified Phase 1 sample size • Clarified eligibility criteria for renal function and QTcF • Clarified DLT language for AEs leading to treatment discontinuation for greater than 3 consecutive weeks
Version 3.0	22 MAR 2021	• Revised secondary objectives with CR/CRh, CR with and without MRD, and DOR • Modification of the dose expansion as dose validation/expansion (Part 1b) to evaluate multiple doses to determine the RP2D
Version 4.0	20 OCT 2021	• Clarified that KO-539 has been determined to be a substrate for the P glycoprotein efflux transporter • Addition of an inclusion criterion for Part 1b dose validation/cohort expansion phase to specify that patients must be concurrently receiving a P glycoprotein inhibitor
Version 5.0	24 JAN 2022	• Removed “serum creatinine <math><2.0\times</math> upper limit of normal (ULN), or if serum creatinine <math>\geq #5="" 2.0\times<="" agency<="" as="" by="" criterion="" from="" inclusion="" li="" math>uln”="" requested="" the=""> • Removed Part 1b inclusion criterion #2 requiring concomitant administration of a P glycoprotein inhibitor during KO-539 treatment • Introduced guidance relative to the monitoring and treatment of DS • Concurrent administration of any systemic anticancer therapies and/or other investigational agents are prohibited, except for the brief periods required for the management of DS with hyperleukocytosis </math>\geq>
Version 6.0	12 MAY 2022	• Added that anticipated individual patient duration on study is from enrollment until the lack of clinical benefit or tolerability • Added exploratory objectives and endpoints to assess plasma concentrations of ziftomenib and metabolite(s) and to evaluate biomarkers potentially related to ziftomenib activity • Updated the sample size for the Phase 1 portion of the study • Updated concomitant therapies section to allow the use of medication in the context of DS and recommend the use of H2 antagonists instead of PPIs • Added guidance on resuming ziftomenib post-transplant

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Protocol version	Date	Key Changes
Version 7.0	06 OCT 2022	- Added R/R <i>NPM1</i>-m AML Phase 2 cohort, removed mention of KMT2A-r Phase 2 evaluation - Updated background information including benefit/risk, toxicology, RP2D
Version 8.0	11 MAY 2023	- Added sub-studies 1 (midazolam DDI), 2 (itraconazole DDI), and 3 (ALL) - Added information relating to ziftomenib treatment in post-transplant maintenance - Removed central confirmation of local <i>NPM1</i> mutation and replaced with retrospective testing (to facilitate use for intended companion diagnostic bridging)
Version 9.0	13 SEP 2024	- Inclusion criterion 5a was updated to lower the creatinine clearance requirement from ≥ 50 mL/min to ≥ 30 mL/min and to include the use of the CKD-EPI creatinine-cystatin C equation - Inclusion criterion 6 was updated to require control and maintenance of white blood cell count beyond Cycle 1 Day 1 enrollment as clinically necessary - Exclusion criterion 10 was updated to incorporate specifications regarding CYP3A4 inhibitors and inducers - Formally removed Phase 2 interim analysis (previously removed via SAP) - Added the efficacy analysis set that includes all patients with locally confirmed <i>NPM1</i> mutations who received an initial dose of 600 mg QD ziftomenib. This set includes patients enrolled in both Phase 1b and Phase 2, used for efficacy analysis.

The FDA's Assessment:

The FDA agree with the Applicant's description of protocol amendments.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

This study was conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation guidelines on Good Clinical Practice and regulatory requirements, as applicable.

The Applicant's Position:

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The study was conducted in accordance with Good Clinical Practices, the Declaration of Helsinki, relevant FDA guidelines, and applicable national and/or regional regulations, as per the Code of Federal Regulations, Title 21 (21 CFR 320.25).

Documentation demonstrating compliance with the requirements for the acceptability of foreign data (21 CFR 312.120) is provided in the KO-MEN-001 clinical study report and summary in the NDA Module 2.5. Additional description is provided in Section 8.1.1.

The FDA's Assessment:

The FDA confirms the Applicant's position.

Financial Disclosure

Data:

A financial disclosure review of KO-MEN-001 was conducted and disclosure of financial interests and/or arrangements, including statements of due diligence for the investigators who conducted the study are described in Forms FDA 3454, 3455, and Module 1.3.4.

The Applicant's Position:

The integrity of the data in KO-MEN-001 was not affected by the financial interests of the investigators.

The FDA's Assessment:

The FDA confirms the Applicant's position.

Data Quality and Integrity

The Applicant's Position:

No data integrity concerns during reported during the study.

The FDA's Assessment:

In addition to the original datasets submitted with the cutoff date of 10/28/2024 (SDN 1), the Applicant submitted updated datasets with a later cutoff date of 3/21/2025 (SDN 15). FDA utilized the available raw datasets to adjudicate responses for all the eligible patients from Phase 1 and 2 with the later cutoff date of 3/21/2025. FDA communicated multiple Information Requests to the Applicant to discuss the agreement or disagreement during the adjudication process (SDN 4, 14, 27, 39, and 44). FDA reached alignments on all the eligible participants' response assessments in an updated adrasadj2.xpt (SDN 27). There were 11 patients for whom FDA assessed the remission status or date of remission differently from that reported by the Applicant. These discrepancies are summarized in FDA Table 28. The final adjudicated responses, dates and derived time to event endpoints were in adrsdor2.xpt submitted in SDN 44.

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FDA Table 28. Discrepancy in Best Response Between Applicant and FDA Assessment

Subject ID	Applicant assessment	FDA adjudication	Reason for discrepancy and summary of supporting data
(b) (6)	CRh 01May2024	MLFS 06Feb2024	Count recovery outside of the -7 to +14 day window and next marrow showed relapse
	CRh 13Nov2024	CRi 26Jul2024	Count recovery outside of the -7 to +14 day window and next marrow showed relapse
	CR 22Mar2024	PR 19Apr2024	Aspirate blasts > 5% despite negative flow and molecular MRD. Patient had full count recovery so it meets criteria for PR in ELN 2022.
	CRh 30Oct2023	MLFS 02Oct2023	Count recovery outside of the -7 to +14 day window and next marrow showed relapse
	CR 16May2022	CRh 18Apr2022	Marrow in remission 18Apr2022, CRh count recovery 02May2022, within 14 day window, CRh on 18Apr2022.
	CRh 05Aug2024	CRh 19Aug2024	Count recovery was outside the -7 to +14 day window but the subsequent marrow was still in remission. Date of CRh set to date of partial hematologic recovery.
	CRh 11Oct2023	CRh 23Oct2023	Count recovery between the -7 to +14 day window for the 23Oct2023 marrow.
	CR 30May2024	CR 26Jun2024	The patient had no marrow biopsy performed prior to 26Jun2024. Counts were fully recovered at the time of morphological remission.
	CR 03Oct2023	CR 05Sep2023	Marrow remission on 05Sep 2023 and count recovery on 12Sep2023 so within the -7 to +14 day window
	CR 04Sep2024	CR 27Aug2024	Marrow on 27Aug2024 and count recovery on 04Sep 2024 so within the -7 to +14 day window
	CR 20Nov2023	CR 23Oct2023	Marrow on 23Oct2023 and full count recovery on 30Oct 2023 so within the -7 to +14 day window.

Patient Disposition

Data:

The primary efficacy analysis was performed on the Phase 2 mITT population consisting of 92 patients, with 9 (9.8%) of patients remaining on ziftomenib treatment as of the 28 October 2024 data cutoff date. Of the 92 patients, 34 (37.0%) discontinued treatment due to progressive, 12 (13%) due to lack of efficacy, 17 (18.5%) due to AEs, and 3 (3.3%) due to death. In total, 54 (58.7%) patients discontinued the study due to death, predominantly related to AML. As of 28 October 2024, 26 (28.3%) remained on study.

The Applicant's Position:

The main reasons for treatment discontinuation were related to a patient's underlying disease (progressive disease, lack of efficacy, and AEs). The main reasons for discontinuation from the study was death and withdrawal by patient.

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The FDA's Assessment:

For the Phase 1 portion, no participants from 1a dose escalation had a confirmed *NPM1* mutation; 20 participants from the Phase 1b cohort had a confirmed *NPM1* mutation and received 600 mg of ziftomenib. Therefore, this population (n=20) was considered in the FDA's review of efficacy. In the Phase 2 portion, 92 participants with R/R AML with a confirmed *NPM1* mutation were enrolled and treated with 600 mg of ziftomenib. In total, 112 patients were included in the Pooled Efficacy Cohort, whose disposition is summarized in FDA Table 29 (data cutoff date 28 October 2024).

FDA Table 29. Patient Disposition (Pooled Efficacy Cohort)

N (%)	Phase 1b (N = 20)	Phase 2 (N = 92)	Pooled Efficacy Cohort (N = 112)
End of treatment status			
Discontinued	20 (100)	83 (90)	103 (92)
Ongoing	0	9 (10)	9 (8)
Reason for discontinuation of treatment			
Progressive disease	9 (45)	34 (37)	43 (38)
Adverse event	6 (30)	17 (18)	23 (21)
Lack of efficacy	0	12 (13)	12 (11)
Withdrawal by subject	1 (5)	8 (9)	9 (8)
Death	2 (10)	3 (3)	5 (4)
Physician decision	1 (5)	3 (3)	4 (4)
Other	0	2 (2)	2 (2)
Receipt of alternative anticancer treatments	1 (5)	1 (1)	2 (2)
Symptomatic deterioration	0	2 (2)	2 (2)
Non-compliance	0	1 (1)	1 (1)
End of study status			
Discontinued	18 (90)	66 (72)	84 (75)
Ongoing	2 (10)	26 (28)	28 (25)
Reason for discontinuation from study			
Death	17 (85)	54 (59)	71 (63)
Withdrawal by subject	0	10 (11)	10 (9)
Lost to follow-up	0	1 (1)	1 (0.9)
Other	0	1 (1)	1 (0.9)

Source: FDA Analysis

Protocol Violations/Deviations

Data:

Protocol deviations were reported in 66 (71.7%) patients and were most frequently related to assessments or procedures: 43.5% safety lab assessment, 21.7% efficacy assessment, 14.1%

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safety assessment, 9.8% safety reporting, 8.7% visit not conducted, 6.5% IP dispensing error, 6.5% informed consent. No other deviation was reported by more than 1 patient.

The Applicant's Position:

Major protocol deviations were assessed as not having a significant impact to the safety or patients or study conduct, and the patients involved were continued on study treatment. These deviations are unlikely to impact the overall interpretation of the data.

The FDA's Assessment:

The majority of key protocol violations were laboratory, efficacy, or safety assessments not performed for the Pooled Efficacy Cohort and its Phase 2 subset. The FDA agrees that these deviations were not likely to impact the overall interpretation of the data.

Table of Demographic Characteristics

Data:

A summary of demographic characteristics is presented in Applicant Table 6. Patients in the Phase 2 portion of Study KO-MEN-001 (N=92) had a median baseline age of 69.0 (range, 33 to 84) years, with the majority of patients (64.1%) being over the age of 65 years. Most patients were female (53.3%), White (81.5%), and not Hispanic or Latino (79.3%). Patients were evenly distributed from sites in the US and Canada (48.9%) and Europe and the United Kingdom (51.1%). There were no clinically relevant differences between the Phase 2 mITT population and the supportive Phase 1b EAS population.

Applicant Table 6. Applicant - Patient Demographics: KO-MEN-001 Phase 1b and Phase 2 mITT

	Phase 1b EAS (N=20)	Phase 2 mITT (N=92)
Age, ^a years		
Mean (SD)	62.5 (17.87)	66.3 (11.47)
Median (min, max)	70.5 (22, 86)	69.0 (33, 84)
Age category, n (%)		
18 to <65 years	9 (45.0)	33 (35.9)
≥65 years	11 (55.0)	59 (64.1)
Sex, n (%)		
Male	6 (30.0)	43 (46.7)
Female	14 (70.0)	49 (53.3)

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	Phase 1b EAS (N=20)	Phase 2 mITT (N=92)
Race, n (%)		
White	13 (65.0)	75 (81.5)
Black or African American	1 (5.0)	1 (1.1)
Native Hawaiian/Other Pacific Islander	0	0
Asian	2 (10.0)	2 (2.2)
American Indian/Alaska Native	0	0
Choose not to respond	4 (20.0)	12 (13.0)
Other	0	2 (2.2)
Ethnicity, n (%)		
Hispanic or Latino	0	3 (3.3)
Not Hispanic or Latino	14 (70.0)	73 (79.3)
Choose not to respond	4 (20.0)	11 (12.0)
Not reported	2 (10.0)	5 (5.4)
Region, n (%)		
US and Canada	12 (60.0)	45 (48.9)
EU and UK	8 (40.0)	47 (51.1)
Height, cm		
Mean (SD)	166.03 (10.492)	168.51 (9.526)
Median (min, max)	163.30 (151, 188)	168.00 (149, 184.6)
Weight at Baseline, kg		
Mean (SD)	71.72 (19.800)	73.45 (16.682)
Median (min, max)	68.35 (48, 125.5)	71.05 (41, 111.6)

Source: KO-MEN-001 CSR, Table 14.1.3.4

The Applicant's Position:

The demographic characteristics were representative of and applicable to the known R/R *NPM1*-m AML population. Overall, no clinically relevant differences were observed in baseline patient demographics between the Phase 1b EAS and Phase 2 mITT populations.

The FDA's Assessment:

The baseline demographic characteristics for Pooled Efficacy Cohort are shown in FDA Table

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30. The median age was 69 (range: 22, 86) years old. The summary statistics appear generally similar between the Phase 1 and 2 patients, supporting the pooling of two patient cohorts.

FDA Table 30. Demographic Characteristics (Pooled Efficacy Cohort)

n (%)	Phase 1b (N = 20)	Phase 2 (N = 92)	Pooled Efficacy Cohort (N = 112)
Age, years			
Median (Range)	71 (22, 86)	69 (33, 84)	69 (22, 86)
< 65	9 (45)	33 (36)	42 (38)
≥ 65	11 (55)	59 (64)	70 (63)
Sex			
Female	14 (70)	49 (53)	63 (56)
Male	6 (30)	43 (47)	49 (44)
Race			
White	13 (65)	75 (82)	88 (79)
Asian	2 (10)	2 (2)	4 (4)
Black or African American	1 (5)	1 (1)	2 (2)
Other	0	2 (2)	2 (2)
Unknown	4 (20)	12 (13)	16 (14)
Ethnicity			
Not Hispanic or Latino	14 (70)	73 (79)	87 (78)
Hispanic or Latino	0	3 (3)	3 (3)
Unknown	6 (30)	16 (17)	22 (20)
Geographic Region			
US and Canada	12 (60)	45 (49)	57 (51)
EU and UK	8 (40)	47 (51)	55 (49)

Source: FDA Analysis

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

A summary of baseline disease characteristics in the Phase 2 portion of KO MEN 001 is provided in [Applicant Table 7](#). The baseline disease characteristics in the Phase 2 population of patients in Study KO MEN 001 are reflective of the population of patients with R/R NPM1-m AML seen in clinical practice and are representative of the proposed indication population. The majority of patients in the Phase 2 population at baseline had de novo AML (83.7%), and 16.3% of patients presented with secondary AML, of which 13.0% had antecedent hematological disease-AML. In this population of patients with R/R NPM1-m AML, 64.1% of patients had NPM1 subtype A mutation. At baseline, the most common AML co-mutations included FLT3-ITD mutation (30.4%), DNMT3A mutation (23.9%), and IDH2 mutation (12.0%). Similar proportions of patients in the Phase 1b population had baseline AML types, with no clinically relevant differences observed. In Phase 2, patients had baseline ECOG performance statuses of 0

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(29.3%), 1 (53.3%), or 2 (17.4%). In Phase 2, patients displayed a median bone marrow blast percentage of 39.5% (range 0.5% to 98%) and median peripheral blood blasts of 14.0% (range: 0% to 98%). Extramedullary disease was present in 6 (6.5%) patients at baseline. A large majority (89.1%) of patients were transfusion dependent (TD) at baseline (28 days prior to and 28 days post ziftomenib dose) and 59.8% of patients were TD within 28 days prior to or on the date of the first dose of ziftomenib. The Phase 1b EAS and Phase 2 mITT populations of patients were similar with respect to baseline disease characteristics, except for differences in the percentages of bone marrow and peripheral blasts reported at baseline.

Applicant Table 7: Applicant - Baseline Disease Characteristics: KO-MEN-001 Phase 1b EAS and Phase 2 mITT

	Phase 1b EAS (N=20)	Phase 2 mITT (N=92)
Type of AML, n (%)		
De novo	18 (90.0)	77 (83.7)
Secondary	2 (10.0)	15 (16.3)
AHD-AML	2 (10.0)	12 (13.0)
t-AML	0	3 (3.3)
Baseline disease status, n (%)		
Primary refractory	2 (10.0)	5 (5.4)
Untreated relapsed	8 (40.0)	60 (65.2)
Refractory relapsed	10 (50.0)	27 (29.3)
Baseline ECOG performance status, n (%)		
0	3 (15.0)	27 (29.3)
1	14 (70.0)	49 (53.3)
2	3 (15.0)	16 (17.4)
Bone marrow blasts at baseline, %		
Mean (SD)	52.3 (30.78)	42.2 (28.55)
Median (min, max)	61.5 (6, 91)	39.5 (0.5, 98)
Bone marrow results at screening suboptimal, n (%)	0	9 (9.8)

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	Phase 1b EAS (N=20)	Phase 2 mITT (N=92)
Peripheral blood blasts at baseline, %		
Mean (SD)	35.6 (26.63)	27.3 (30.67)
Median (min, max)	39.5 (0, 79)	14.0 (0, 98)
Extramedullary disease at baseline, n (%)	1 (5.0)	6 (6.5)
Transfusion dependent at baseline, ^a n (%)	17 (85.0)	82 (89.1)
Transfusion dependent within 28 days prior to or on the first dose of ziftomenib, n (%)	11 (55.0)	55 (59.8)
<i>NPM1</i> mutation subtype at baseline, ^b n (%)		
A	13 (65.0)	59 (64.1)
B	0	5 (5.4)
D	4 (20.0)	10 (10.9)
Other	3 (15.0)	7 (7.6)
Unknown	0	11 (12.0)
Mutations at baseline, ^c n (%)		
<i>NPM1</i> -m	20 (100)	92 (100)
FLT3-ITD	4 (20.0)	28 (30.4)
DNMT3A	4 (20.0)	22 (23.9)
IDH2	6 (30.0)	11 (12.0)
SRSF2	3 (15.0)	9 (9.8)
IDH1	2 (10.0)	8 (8.7)
FLT3-TKD	2 (10.0)	7 (7.6)

Source: KO-MEN-001 CSR, Table 14.1.4.4 and Table 14.1.4.4.1

A summary of prior antineoplastic therapies in the Phase 2 mITT portion of KO MEN 001 are presented in [Applicant](#) Table 8. Patients reported a median number of prior lines of therapy at baseline of 2.0 (range 1 to 7), with 58.7% receiving prior venetoclax and 23.9% receiving prior stem cell transplantation. This baseline number of prior therapies confirms that the Phase 2 patient population, on average, had already failed on at least 2 prior therapies and were starting on their third or greater line of treatment for their disease. In the Phase 1b patient population, the median number of prior therapies at baseline was identical to the Phase 2 population, lending additional confidence to the similarity of these populations for comparison as a supportive efficacy analysis population.

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Applicant Table 8: Applicant - Prior Antineoplastic Therapies: KO-MEN-001 Phase 1b EAS and Phase 2 mITT

	Part 1b EAS (N=20)	Phase 2 mITT (N=92)
Prior stem cell transplantation, n (%)	4 (20.0)	22 (23.9)
Prior venetoclax, n (%)	13 (65.0)	54 (58.7)
Prior menin inhibitor, n (%)	0	1 (1.1)
Number of prior lines of therapy		
Mean (SD)	2.7 (1.69)	2.2 (1.25)
Median (min, max)	2.0 (1, 7)	2.0 (1, 7)
Number of prior lines of therapy, n (%)		
1	5 (25.0)	32 (34.8)
2	7 (35.0)	30 (32.6)
≥3	8 (40.0)	30 (32.6)
3	2 (10.0)	16 (17.4)
4	4 (20.0)	10 (10.9)
5	0	2 (2.2)
6	1 (5.0)	1 (1.1)
7	1 (5.0)	1 (1.1)

Source: KO-MEN-001 CSR, Table 14.1.5.4

The Applicant's Position:

Consistent with the expected patient population, the study enrolled patients who were heavily pre-treated and relapsed and/or refractory. These baseline disease characteristics and the prior antineoplastic therapies reflect those of patients with R/R NPM1-m AML, including involvement of additional high-risk co-mutations, expected bone marrow and peripheral blood blast counts, and the number of prior antineoplastic therapies.

The FDA's Assessment:

Most participants (83%) had a performance status of 0-1, de novo AML (85%), and prior use of venetoclax (60%). The median number of prior lines of therapy is 2 (range: 1, 7) and 23% had prior HSCT (FDA Table 31). There were 59% patients who were transfusion dependent at baseline.

FDA Table 31. Disease Characteristics (Pooled Efficacy Cohort)

n (%)	Phase 1b	Phase 2	Pooled Efficacy

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Version date: March 1, 2024 (ALL NDA/ BLA reviews)

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	(N = 20)	(N = 92)	Cohort (N = 112)
Baseline ECOG			
0	3 (15)	27 (29)	30 (27)
1	14 (70)	49 (53)	63 (56)
2	3 (15)	16 (17)	19 (17)
Type of AML at baseline			
De Novo	18 (90)	77 (84)	95 (85)
Secondary	2 (10)	15 (16)	17 (15)
Bone marrow blasts at baseline %			
Mean (SD)	52 (31)	42 (29)	44 (29)
Median (range)	62 (6, 91)	40 (5, 98)	44 (5, 98)
<i>NPM1</i> mutation subtype at baseline			
A	13 (65)	59 (64)	72 (64)
B	0	5 (5)	5 (4)
D	4 (20)	10 (11)	14 (13)
Other	3 (15)	7 (8)	10 (9)
Unknown	0	11 (12)	11 (10)
Comutation at baseline			
<i>FLT3</i> -ITD	4 (20)	28 (30)	32 (29)
<i>FLT3</i> -TKD	2 (10)	7 (8)	9 (8)
<i>DNMT3A</i> -m	4 (20)	22 (24)	26 (23)
<i>IDH2</i> -m	6 (30)	11 (12)	17 (15)
<i>IDH1</i> -m	2 (10)	8 (9)	19 (17)
Prior Venetoclax	13 (65)	54 (59)	67 (60)
Prior HSCT	4 (20)	22 (24)	26 (23)
Median number of prior lines (range)	2 (1, 7)	2 (1, 7)	2 (1, 7)
Transfusion dependent	11 (55)	55 (60)	66 (59)

Source: FDA Analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

The mean (SD) and median relative dose intensity were 90.37% (15.318) and 99.03% in the Phase 2 mITT population used for primary efficacy and safety analyses.

Concomitant Medications

All 92 patients in Phase 2 reported a concomitant medication. The most frequently used medications were typical of those used by the patient population under study and included antibacterials for systemic use (96.7%), antimycotics for systemic use (94.6%), and antivirals for systemic use (82.6%).

The Applicant's Position:

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Treatment compliance was well maintained with high median relative dose intensity. Concomitant medication use was representative of an AML patient population.

The FDA's Assessment:

The treatment duration of ziftomenib was short with median duration of 2.2 months (range: 0.07, 21.5 months) in the Pooled Efficacy Cohort, with only 21 (18.8%) patients having received treatment for at least 6 months. These results were similar between the Phase 1 and 2 patients, as the median of treatment duration was 2.4 (range: 0.5, 14.7) and 2.2 (range: 0.07, 21.5) months.

Clinical TL Comment: Of note, the time required to achieve remission is often delayed when non-cytotoxic, targeted agents are used for the treatment of R/R AML, as shown in Le, et al.¹² In this analysis, the median time to remission (CR + CRh) was 2.8 months, and the median time on treatment was 4.2 months for these agents. Given the median duration of treatment of only 2.2 months in this study, this short treatment duration may affect the observation of the efficacy endpoints including response rate and durability.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The primary efficacy endpoint in the KO-MEN-001 Phase 2 cohort was CR/CRh rate. At the protocol-specified planned primary analysis with a data cutoff of 28 Oct 2024, the study met the primary endpoint with statistical significance, demonstrating a CR/CRh rate of 21.7% (95% CI: 13.8, 31.6; p=0.0058). The CR/CRh rate compared favorably to the null hypothesis of 12% based on historical data. Results are presented in Applicant Table 9.

Subgroup analysis of CR/CRh rate based on factors such as geographic location, prior therapies, ECOG score and others aligned with the primary Phase 2 data, showing no clinically meaningful or statistically significant differences in CR/CRh rates between the predefined subgroups as evidenced by overlapping error bars compared to the overall CR/CRh results (Applicant Figure 2).

Among 54 patients with prior venetoclax exposure, clinical responses indicated that ziftomenib maintained activity in patients who relapse after or were refractory to prior venetoclax. The CR/CRh rate was 22.2% (95% CI: 12.0%, 35.6%) in patients with prior venetoclax exposure compared with 21.1% (95% CI: 9.6%, 37.3%) in patients without prior venetoclax exposure. This represents a notable improvement over published responses which suggest venetoclax failure is associated with poor response to follow-on therapy (Gangat et al, 2023; Maiti et al, 2021). Although there was a trend toward differential response rates by region (North America

¹² Le, RQ, et al (2024). Complete remission with partial hematologic recovery as a palliative endpoint for treatment of acute myeloid leukemia. Blood; 144:206-15.

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vs Europe), this regional difference is likely due to the addition of new European clinical sites in the Phase 2 study with investigators who had no prior experience with ziftomenib and its unique mechanism of action requiring up to 3 cycles or more to achieve best response, thus leading to early discontinuations until the investigators became familiar with ziftomenib response kinetics.

Applicant Table 9: Applicant - Primary Efficacy: Remission Rate

Endpoints	Part 1b EAS (N=20)	Phase 2 mITT (N=92)
CR/CRh, n (%)	7 (35.0)	20 (21.7)
95% CI	(15.4, 59.2)	(13.8, 31.6)
p-value	N/A	0.0058
MRD negativity rate	4/5 (80.0)	9/14 (64.3)
95% CI	(28.4, 99.5)	(35.1, 87.2)
CR rate, n (%)	7 (35.0)	13 (14.1)
95% CI	15.4 (59.2)	(7.7, 23.0)
CRh rate, n (%)	0	7 (7.6)
95% CI	0	(3.1, 15.1)
CRc rate (CR+CRh+CRp+CRi), n (%)	8 (40.0)	24 (26.1)
95% CI	(19.1, 63.9)	(17.5, 36.3)
MRD negativity rate	4/6 (66.7)	10/16 (62.5)
95% CI	(22.3, 95.7)	(35.4, 82.7)

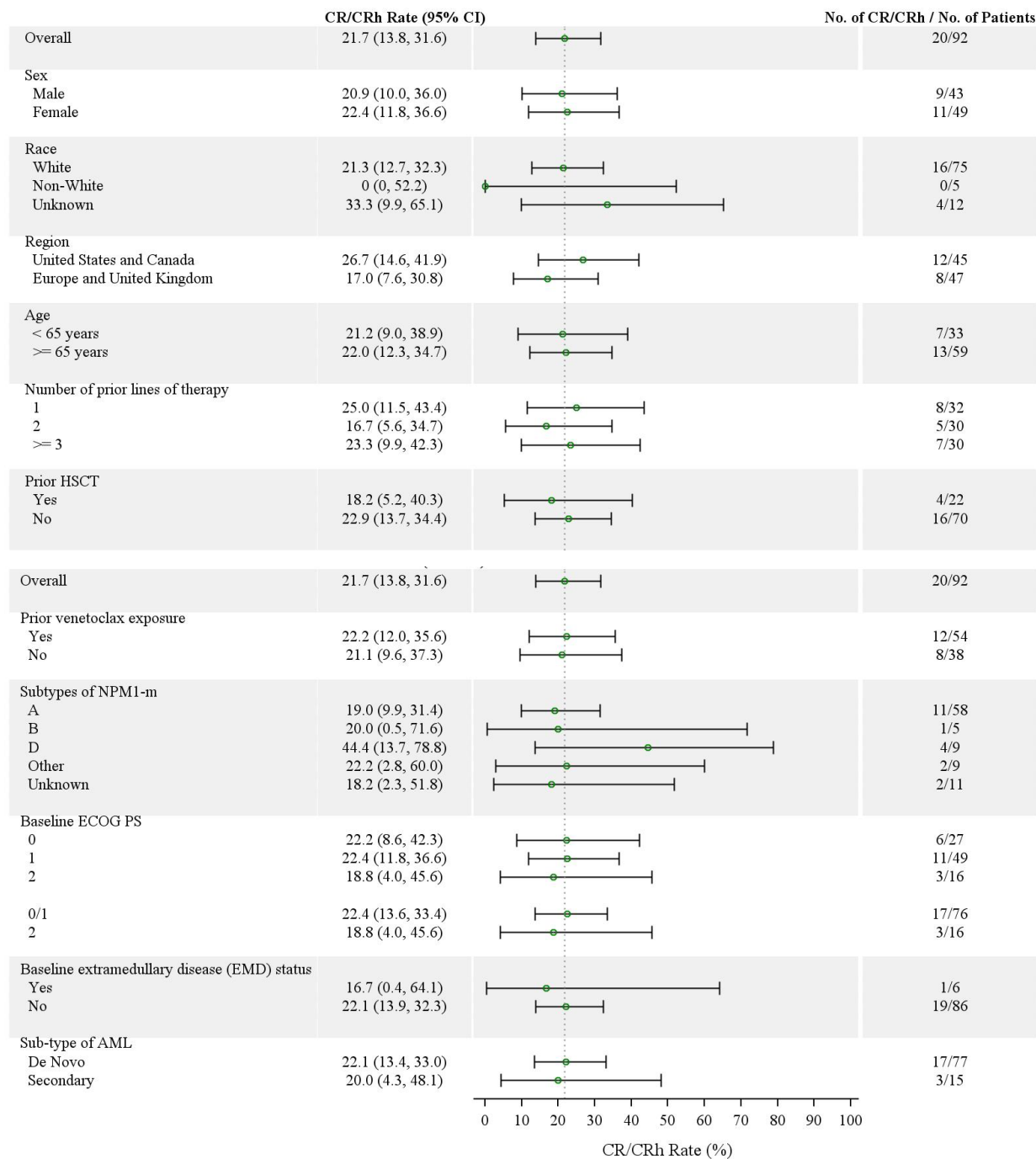
Source: Module 2.7.3, Table 8

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Applicant Figure 2: Applicant - Forest Plot of CR/CRh Rate by Subgroup (Phase 2 mITT)



Source: KO-MEN-001 CSR, Figure 14.2.7.1

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The Applicant's Position:

In heavily pre-treated patients with R/R *NPM1*-m AML, ziftomenib treatment induced a clinically meaningful response to treatment. The KO-MEN-001 Phase 2 study met the primary efficacy endpoint for CR/CRh rate (21.7%) at the planned primary analysis.

In the Phase 2 mITT population, CR responses occurred in 14.1% (95% CI: 7.7, 23.0) of patients (historical control of low-intensity chemotherapy from 2% to 6%; Perl et al, 2019; Issa et al, 2023) and accounted for approximately two-thirds of the overall CR/CRh response rate (21.7%). Sixty percent of patients (6 of 10 patients) with a BOR of CR who were locally evaluated for MRD achieved MRD-. In patients who achieved a CR/CRh response and were tested for MRD in the Phase 2 population (n=14), there were 9 (64.3%) patients who achieved MRD- with ziftomenib 600 mg QD treatment, demonstrating a deep and robust efficacy response to treatment. These data demonstrate that ziftomenib's pharmacologic activity against the menin-MLL(KMT2A) complex is sufficient to induce deep clinical responses in heavily pretreated patients who have been refractory to or relapsed following multiple lines of therapy, thus validating the menin protein as a critical drug target in these patients.

The positive results of CR/CRh were supported by 4 additional patients who achieved CRi in the Phase 2 mITT population leading to a CRc rate of 26.1% (95% CI: 17.5, 36.3; Applicant Table 9). While not a regulatory endpoint, achievement of CRi indicates positive treatment effect on underlying disease and clinical benefit. Additionally, MRD- based on local readings was observed in 62.5% (10 of 16 patients with available MRD data) in patients who achieved CRc.

In the Phase 1b EAS population, 35% (95% CI: 15.4%, 59.2%) of patients achieved CR/CRh (Applicant Table 9). An additional patient in the Phase 1b EAS population achieved a BOR of CRi/complete remission with incomplete platelet recovery (CRp), rendering a CRc rate of 40%. The treatment effects in the Phase 1b EAS population (N=20) population confirmed the clinically meaningful response rates observed in the Phase 2 mITT population.

In totality, these findings on the primary efficacy analysis are evidence that ziftomenib provides a clinically meaningful therapeutic option for patients with R/R *NPM1*-m AML for the proposed indication.

The FDA's Assessment:

The results of response rate based on the FDA's adjudicated responses are summarized in FDA Table 32 for the Pooled Efficacy Cohort. The CR + CRh rates were similar between the Phase 1b and 2 cohorts, although the lower bound of 95% CI excluded the proposed benchmark of 12% only in the Phase 1b and the Pooled Efficacy Cohorts.

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FDA Table 32. Summary of Response Rate

n (% [95% CI])	Phase 1b (N = 20)	Phase 2 (N = 92)	Pooled Efficacy Cohort (N = 112)
CR + CRh	7 (35%) [15.4%, 59.2%]	17 (18.5%) [11.1%, 27.9%]	24 (21.4%) [14.2%, 30.2%]
CR	6 (30%) [11.9%, 54.3%]	13 (14.1%) [7.7%, 23%]	19 (17.0%) [10.5%, 25.2%]
CRh	1 (5%) [0.1%, 24.9%]	4 (4.3%) [1.2%, 10.8%]	5 (4.5%) [1.5%, 10.1%]

Source: FDA analysis

Statistical TL’s Comment: The null rate of 12% specified for the Phase 2 Cohort was based loosely on historical data of a different endpoint (12% CR/CRi as reported in for a population of patients who mostly had ≥ 2 or more prior therapies). Thus, its relevance to the studied population is unclear. However, clinical trials are evaluated based on whether they meet their planned objectives or not. After adjudication, the Phase 2 Cohort did not meet its pre-specified objective to rule out a CR + CRh rate of 12%. While the initial results excluded this threshold, the impact of adjudication on the inference raises questions about the robustness of the results.

The 95% confidence interval for CR + CRh in the Pooled Efficacy Cohort excludes 12%. This provides a more comprehensive experience and appears to confirm the initial inference by the Applicant. This analysis does not account for the multiple-testing nature of this inference.

A more natural inference framework for such evidence synthesis might be the Bayesian framework. While the Phase 1b and Phase 2 populations are similar, it is possible that they differ in meaningful ways such that pooling may not reflect a homogenous population. In this scenario, the Phase 1b results could be considered in a prior distribution with varying levels of relevance to the Phase 2 population. The strength of evidence utilizing in a prior distribution is often characterized by the effective sample size (ESS). FDA Table 33 considers such prior distributions at varying levels of informativeness, with 100% ESS reflecting the scenario where the prior distribution reflects n=20 patients worth of data.

FDA Table 33. Bayesian Analysis of Phase 1b/2 Data in KO-MEN-001 Under Various Levels of Borrowing

Prior Type	Prior Distribution	Posterior Distribution	Posterior Mean	Posterior 95% CI	P(p > 0.12) ¹
100% ESS	Beta(7, 13)	Beta(24, 88)	0.214	(0.147, 0.292)	0.9946
50% ESS	Beta(3.5, 6.5)	Beta(20.5, 81.5)	0.201	(0.137, 0.276)	0.9854
25% ESS	Beta(1.75, 3.25)	Beta(18.75, 78.25)	0.193	(0.129, 0.267)	0.9738
Non-informative	Beta(1, 1)	Beta(18, 76)	0.191	(0.125, 0.268)	0.9651
Improper Prior	Beta(0.001, 0.001)	Beta(17.001, 75.001)	0.185	(0.121, 0.260)	0.9516

¹p is the probability of a patient achieving CR + CRh

These results suggest that the probability of the CR + CRh rate exceeding 12% is high for all scenarios, regardless of how much information is borrowed from Phase 1b. While there is no standard cutoff for Bayesian analyses to demonstrate “significance,” one might consider a

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decision rule such as $Pr(p < 0.12) < 0.025$. This is the case for 100% and 50% ESS. In other words, as long as the Phase 1b data are considered at least relevant enough to borrow half of the information, the data suggest that there is over a 97.5% probability that the CR + CRh rate is above 12%.

Note that for the population of patients with NPM1 mutated AML, the inclusion criteria are identical. While there are minor differences in the baseline characteristics and response rates, no overt signals suggest that the populations are meaningfully different. Pooling appears to be justified and even under scenarios in which the Phase 1b data are not directly applicable to Phase 2, the probability that the CR + CRh rate exceeds 12% is high.

It should be noted that while it is helpful to contextualize the total data relative to the pre-specified efficacy threshold, this threshold is modest. Merely excluding a 12% CR + CRh rate is not sufficient to establish substantial evidence of efficacy on its own. Products intended to establish efficacy based on CR + CRh should also be tolerable, have sufficient durability of response, and a meaningful rate of transfusion independence. These measures are discussed below.

The subgroup analyses by demographic characteristics and baseline disease characteristics show that treatment effect was generally observed across all subgroups (see FDA Table 34).

FDA Table 34. Summary of Response Rate (CR + CRh) by Subgroup (Pooled Efficacy Cohort)

	Pooled Efficacy Cohort (N = 112)	
	n/N	CR + CRh rate (95% CI)
Age, years		
< 65	8/42	19% (16%, 55%)
≥ 65	16/70	23% (16%, 55%)
Sex		
Female	15/63	24% (41%, 81%)
Male	9/49	18% (41%, 81%)
Race		
White	18/88	20% (23%, 30%)
Asian, Black, Other	2/8	25% (3%, 65%)
Unknown	4/16	25% (7%, 52%)
Geographic region		
US and Canada	15/57	26% (19%, 59%)
EU and UK	9/55	16% (19%, 59%)
Number of prior lines		
1	11/37	30% (16%, 47%)
2	6/37	16% (6%, 32%)
3+	7/38	18% (8%, 34%)
Prior Venetoclax		

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Yes	12/67	18% (10%, 29%)
No	12/45	27% (15%, 42%)
Prior HSCT		
Yes	3/26	12% (2%, 30%)
No	21/86	24% (16%, 35%)
NPM1 mutation subtype at baseline		
A	13/72	18% (10%, 29%)
B	1/5	20% (1%, 72%)
D	6/14	43% (18%, 71%)
Other	2/10	20% (3%, 56%)
Unknown	2/11	18% (2%, 52%)
Baseline ECOG		
0, 1	21/93	23% (68%, 97%)
2	3/19	16% (68%, 97%)
2		
Type of AML at baseline		
De Novo	21/95	22% (14%, 32%)
Secondary	3/17	18% (4%, 43%)
Comutation (Phase 2 Cohort Only)		
<i>FLT3</i> -ITD	4/28	14% (4%, 33%)
<i>FLT3</i> -TKD	3/7	43% (10%, 82%)
<i>DNMT3A</i> -m	6/22	27% (11%, 50%)
<i>IDH1</i> -m	4/8	50% (16%, 84%)
<i>IDH2</i> -m	3/11	27% (6%, 61%)

Source: FDA Analysis

Clinical TL Comment: Of interest, the CR + CRh rate appears to be numerically higher in study participants with a Type D NPM1 mutation. The interpretation of this is limited by small overall numbers, but this will be interesting to investigate in the postmarket setting and in the future randomized Phase 3 study.

*The impact of comutation on the efficacy of ziftomenib was explored as a subgroup analysis in the Phase 2 cohort, as this data was not directly collected at the time of relapse prior to initiation of Phase 2. While the FDA acknowledges the small sample size of each individual comutation subgroup, the presence of a *FLT3*-ITD appears to portend an inferior response rate, compared to the other mutations, which were generally in line with the broader treatment population. With that being said, the broad confidence interval around the response rate of the *FLT3*-ITD population includes the point estimate for the broader population, and the recommended indication ensures that patients should have received *FLT3* targeted therapies prior to ziftomenib. No other mitigation strategy is warranted at this time.*

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Efficacy Results – Secondary and other relevant endpoints

Data:

Duration of Response and Time to Response

Duration of Response (DOR) and time to response are summarized in Applicant Table 10. As of the cutoff date of 28 October 2024, the median follow-up time in the Phase 2 mITT population was 4.1 months (range: 0.1 to 18.4 months). The data cutoff occurred when the 85th patient completed 6 cycles. This positive CR/CRh response was achieved in a median time to CR/CRh response of 2.8 months (95% CI: 1.0, 15.0) and a subsequent median duration of CR/CRh response of 3.7 months (95% CI: 1.9 to 7.4) for a median period of disease control of greater than 6 months for CR/CRh. The median time to CR/CRh for patients treated with ziftomenib in the Phase 2 mITT population is similar to the median time to CR/CRh observed with other differentiating agents, such as IDH inhibitors (approximately 2.7 months; DiNardo et al, 2018). This is, in part, because menin inhibitors are not directly cytotoxic, but instead require the terminal differentiation of leukemic blasts, which are subsequently cleared via scheduled apoptosis. Therefore, a best response of CR/CRh to ziftomenib is the result of an evolution of the response over time where the patient has consistent disease control with blast clearance prior to CR/CRh. In patients who achieved a CR/CRh response, the Kaplan Meier (KM) probability of maintaining a CR/CRh response to treatment at 3 and 6 months was 57.3% and 33.5%, respectively, which provides evidence to the durability of response to ziftomenib treatment. Due to the potential for instability of KM estimates at lower sample sizes or significant censoring, an ad hoc restricted mean for each of the response durations was performed in accordance with FDA guidance. The restricted mean duration of CR/CRh response was 4.7 months (95% CI: 2.9, 6.5), validating the duration of response estimates as clinically meaningful.

The median time to achieving a response of CR was 2.8 months (95% CI: 1.8, 3.8) and a median duration of CR (3.7 months [95% CI: 2.8, 7.4]) similar to those seen with CR/CRh responses in patients treated with ziftomenib.

The median time to achieve CRc was also 2.8 months (95% CI: 0.8, 4.6) similar to that observed with the response of CR/CRh, and a median duration of CRc of 4.6 months (95% CI: 2.8, 11.4). These data suggest a median disease control period of greater than 7 months in patients who achieve a CRc response.

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Applicant Table 10: Applicant - Summary of Duration of Response and Time to Response

Endpoints	Part 1b EAS (N=20)	Phase 2 mITT (N=92)
Duration of CR/CRh (months)		
Median DOR (95% CI)	5.6 (0.6, 8.1)	3.7 (1.9, 7.4)
Range	0.0 ⁺ , 13.8	0.0 ⁺ , 11.4
Duration of CR/CRh KM estimates, (95% CI)		
At 3 Months	57.1 (17.2, 83.7)	57.3 (30.0, 77.3)
At 6 Months	42.9 (9.8, 73.4)	33.5 (11.2, 57.8)
At 9 Months	14.3 (0.7, 46.5)	22.3 (4.4, 48.7)
Time to CR/CRh; median (range), months	2.3 (0.9, 7.4)	2.8 (1.0, 15.0)
Restricted mean DOR (95% CI), months		
Truncated at the time when at least 10% of patients remain at risk	5.5 (2.2, 8.8)	4.7 (2.9, 6.5)
Duration of CR (months)		
Median DOR (95% CI)	5.6 (0.6, 8.1)	3.7 (2.8, 7.4)
Time to CR; median (range), months	2.3 (0.9, 7.4)	2.8 (1.8, 3.8)
Duration of CRh, (months)		7 (7.6)
Median DOR (95% CI)	0	1.9 (1.0, NE)
Time to CRh; median (range), months	NE	3.7 (1.0, 15.0)
Restricted mean DOR (95% CI), months		
Truncated at the time when at least 10% of patients remain at risk	N/A	5.9 (1.5, 10.2)
Duration of CRc, (months)		24 (26.1)
Median DOR (95% CI)	6.6 (1.0, 13.8)	4.6 (2.8, 11.4)
Time to CRh; median (range), months	2.0 (0.9, 7.4)	2.8 (0.8, 4.6)
Restricted mean DOR (95% CI), months		
Truncated at the time when at least 10% of patients remain at risk	6.9 (3.5, 10.2)	5.7 (3.8, 7.6)

Source: KO-MEN-001 CSR, Tables 14.2.2.4, 14.2.1.4, and 14.2.3.4

Best Overall Response and Overall Response Rate

Best overall response (BOR) and overall response rate (ORR) are summarized in Applicant Table 11. The best overall responses included 13 patients (14.1%) with CR, 7 patients (7.6%)

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with CRh, 4 patients (4.3%) with CRi, 5 patients (5.4%) with MLFS, and 1 patient (1.1%) with PR.

In the Phase 2 mITT population, The CRc rate was 26.1% and the ORR was 32.6% (95% CI: 23.2, 43.2), with a duration of overall response of 4.6 months (95% CI: 2.8, 7.4).

Overall response was defined as a patient achieving a BOR of CR, CRh, CRi, CRp (in Part 1b), MLFS, or PR. In the Phase 2 mITT population, ORR was achieved in 30 (32.6% [95% CI: 23.2, 43.2]) patients and a median duration of overall response of 4.6 months (95% CI: 2.8, 7.4). This included 2 patients with responses of MLFS and PR prior to HSCT who improved to CR MRD⁻ post-HSCT. Overall 10 of 22 (45.5%) patients, who achieved ORR and had MRD assessed, achieved MRD⁻. Patients achieved a response to treatment quickly at a median of 1.9 months (95% CI: 0.8, 3.7) and maintained that response to ziftomenib treatment for a median duration of 4.6 months (95% CI: 2.8, 7.4), suggesting a median treatment ORR benefit exceeding 6 months in this patient population with R/R *NPM1*-m AML.

Applicant Table 11: Applicant - Best Overall Response and Overall Response Rate

	Part 1b EAS (N=20)	Phase 2 mITT (N=92)
Best Overall Response, [n (%)]		
CR	7 (35.0)	13 (14.1)
CRh	0	7 (7.6)
CRi	1 (5.0)	4 (4.3)
MLFS	1 (5.0)	5 (5.4)
PR	0	1 (1.1)
Stable Disease/No Response/Clinical Benefit/ Progressive Disease	9 (45.0)	46 (50.0)
Not Evaluable	2 (10.0)	16 (17.4)
Overall Response Rate (CR + CRh + Cri + CRp + MLFS + PR), [n (%)]		
n (%)	9 (45.0)	30 (32.6)
95% CI	(23.1, 68.5)	(23.2, 43.2)
Duration of overall response, months, median (95% CI)	5.6 (2.5, 13.8)	4.6 (2.8, 7.4)
Time to overall response, months, median (range)	1.7 (0.9, 4.8)	1.9 (0.8, 3.7)
MRD-		
Rate n/m (%)	4/7 (57.1)	10/22 (45.5)
95% CI ³	(18.4, 90.1)	[18.4, 90.1]

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Source: KO-MEN-001 CSR, Tables 14.2.1.4 and 14.2.9.2

Transfusion Independence

Conversion to transfusion independent and maintenance of transfusion independence are summarized in Applicant Table 12 for the Phase 2 mITT population and the supportive Phase 1b EAS population. In the Phase 2 mITT population, among the 82 patients who were dependent on RBC and/or platelet transfusions at baseline, 16 (19.5%) patients became transfusion independent (TD to TI) for both RBC and platelets, and 2 of 10 (20.0%) patients maintained their TI postbaseline (TI to TI). Further assessment of TI conversion and maintenance rates by RBC and platelets is provided in Applicant Table 12.

Comparing transfusion conversion and maintenance results to response for either RBC or platelet transfusions, nearly all patients who were treatment responders achieved TI postbaseline. Of note, 3 of the 4 patients with a BOR of CRi did not require platelet transfusions for 47 days, 44 days, and 38 days. The Phase 1b results provide supportive evidence of the ziftomenib treatment effect on transfusion requirements in this patient population, as displayed by the overall pooled populations. Taken together, these results provide evidence that ziftomenib treatment is nonmyelosuppressive and provides added clinical benefit beyond treatment response criteria, such as reduced bleeding risk, decreased fatigue, and maintained independence in a patient's daily activities.

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Applicant Table 12: Applicant - Transfusion Conversion and Maintenance Rates

Category	Part 1b EAS (N=20)	Phase 2 (N=92) mITT
Postbaseline transfusion of RBC		
Transfusion conversion (TD to TI) rate, n/m (%)	6/17 (35.3)	17/75 (22.7)
95% CI	(14.2, 61.7)	(13.8, 33.8)
Transfusion maintenance (TI to TI) rate, n/m (%)	1/3 (33.3)	2/17 (11.8)
95% CI	(0.8, 90.6)	(1.5, 36.4)
Postbaseline transfusion of platelets		
Transfusion conversion (TD to TI) rate, n/m (%)	4/14 (28.6)	11/71 (15.5)
95% CI	(8.4, 58.1)	(8.0, 26.0)
Transfusion maintenance (TI to TI) rate, n/m (%)	2/6 (33.3)	8/21 (38.1)
95% CI	(4.3, 77.7)	(18.1, 61.6)
Postbaseline transfusion of RBC or platelets		
Transfusion conversion (TD to TI) rate, n/m (%)	5/17 (29.4)	16/82 (19.5)
95% CI	(10.3, 56.0)	(11.6, 29.7)
Transfusion maintenance (TI to TI) rate, n/m (% ^c)	1/3 (33.3)	2/10 (20.0)
95% CI ^b	(0.8, 90.6)	(2.5, 55.6)

Source: KO-MEN-001 CSR, Table 14.2.4.1.4

Overall Survival

In the Phase 2 portion of Study KO-MEN-001 with a median of 2 prior therapies at baseline, the median OS was 6.6 months (95% CI: 3.6, 8.6) (Applicant Table 13). In this patient population, the KM probabilities of OS at 6 or 12 months were estimated to be 53.0% (95% CI: 41.6, 63.1) and 30.6% (95% CI: 19.8, 42.1), respectively. At 18 months, the OS probability was 28.0% (95% CI: 17.3, 39.8), suggesting a prolonged survival benefit in over one-quarter of patients in this R/R *NPM1*-m AML population. The median OS and KM probabilities observed in the Phase 1b EAS and pooled populations were similar to those seen in the Phase 2 mITT population with no clinically relevant differences observed.

Although Study KO-MEN-001 is a single-arm Phase 2 study, the 6.6-month median OS underscores the clinical benefit afforded by ziftomenib monotherapy in R/R *NPM1*-m AML patients.

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Applicant Table 13: Applicant - Overall Survival

Category	Part 1b EAS (N=20)	Phase 2 mITT (N=92)
OS, months ^a		
Median	5.6	6.6
95% CI	(2.1, 12.1)	(3.6, 8.6)
OS probability, % (95% CI) ^b		
At 3 months	65.0 (40.3, 81.5)	70.9 (60.0, 79.3)
At 6 months	45.0 (23.1, 64.7)	53.0 (41.6, 63.1)
At 9 months	40.0 (19.3, 60.0)	38.4 (27.1, 49.5)
At 12 months	30.0 (12.3, 50.1)	30.6 (19.8, 42.1)
At 15 months	25.0 (9.1, 44.9)	28.0 (17.3, 39.8)
At 18 months	25.0 (9.1, 44.9)	28.0 (17.3, 39.8)

Source: KO-MEN-001 CSR, Table 14.2.6.4

The Applicant's Position:

The primary efficacy endpoint in the KO-MEN-001 Phase 2 cohort was CR/CRh rate, and the key secondary endpoint was duration of remission. This positive CR/CRh response was achieved in a median time to CR/CRh response of 2.8 months (95% CI: 1.0, 15.0) and a subsequent median duration of CR/CRh response of 3.7 months (95% CI: 1.9 to 7.4) for a median period of disease control of greater than 6 months for CR/CRh. Responders maintained response for up to 11.4 months. The restricted mean duration of CR/CRh response was 4.7 months (95% CI: 2.9, 6.5), validating the aforementioned duration of response estimates as clinically meaningful.

Patients who achieve CR/CRh are considered to have a clinically meaningful reduction in their disease status by displaying less than 5% blasts in bone marrow and full recovery of neutrophils and platelets (or partial recovery, CRh), which reduces infection and bleeding risks, decreases transfusion-related complications, and improves quality of life. While CRi is not a regulatory endpoint in this setting, the aforementioned benefits are also seen in patients achieving CRi (contributing to CRc), as patients with AML and persistent neutropenia are already in a high-risk category for infection and are recommended to receive antimicrobial prophylaxis carrying their own inherent risks. The additional secondary endpoints support the primary endpoint with regards to overall clinical benefit. The CRc (26.1%) and ORR (32.6%) rates further qualify the clinical importance of the durable CR/CRh rate of 27.1% demonstrated in KO-MEN-001 Phase 2. 16 (19.5%) patients became transfusion independent (TD to TI) for both RBC and platelets, and 2 of 10 (20.0%) patients maintained their TI postbaseline (TI to TI). The rates of conversion to (19.5%) and maintenance of (20%) transfusion independence corroborate the primary efficacy

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results (CR/CRh rate of 21.7%), providing additional evidence of clinical benefit in this palliative setting.

Patients with *NPM1*-m AML who relapse have a dismal prognosis, with demonstrable worsening of survival outcomes with each subsequent line of therapy, as low as 3.5 months (Issa et al, 2023). Based on a retrospective analysis of 206 *NPM1*-m AML patients, median RFS was as low as 3.3 months in the R/R setting. While *NPM1*-m AML may be associated with a more favorable prognosis compared with other genetic subgroups in the newly diagnosed setting, there was no significant difference in RFS or OS among R/R patients with *NPM1*-m AML compared with *NPM1* wt (Issa et al, 2023), demonstrating that any positive prognostic value associated with *NPM1*-m at diagnosis is lost in the R/R setting. In the Phase 2 mITT population with a median of 2 prior therapies at baseline, the median OS of 6.6 months was longer than that of patients who received multiagent approaches. Although KO-MEN-001 is a single arm trial, the OS outcomes suggest a prolonged survival benefit in patients receiving ziftomenib monotherapy.

The secondary efficacy results were generally consistent between the Phase 2 mITT primary efficacy analysis and the supportive Phase 1b EAS population, providing further confirmatory evidence of the Phase 2 results. Ziftomenib 600 mg QD monotherapy provides temporary disease control as a palliative treatment in the proposed indicated patient population, demonstrating relief from disease burden.

The FDA's Assessment:

Results of DOR are summarized in FDA Table 35 for the 24 participants from the Pooled Efficacy Cohort who achieved a best response of CR or CRh. Due to the small number of participants achieving a best response of CRh (i.e., 1 in Phase 1b and 4 in Phase 2), observed DoCRh is reported in this summary table and in the USPI. Similarly, given the low CR + CRh rate overall, the estimated Do(CR + CRh) and DoCR have large variation and should be interpreted with caution.

FDA Table 35. Summary of Duration of Response (DoR)

	Phase 1b (N = 20)	Phase 2 (N = 92)	Pooled Efficacy Cohort (N = 112)
Median Do(CR + CRh)	N = 7	N = 17	N = 24
Median (range), months	5.6 (1.0, 13.8)	4.6 (0.0+ to 14.7+)	5.0 (0.0+ to 14.7+)
95% CI	(1.0, NE)	(2.8, 8.3)	(1.9, 8.1)
Median DoCR	N = 6	N = 13	N = 19
Median (range), months	5.6 (1.0 to 13.8)	4.6 (0.8 to 14.7+)	5.0 (0.8 to 14.7+)
95% CI	(1.0, NE)	(2.8, 8.3)	(2.8, 8.1)
Observed DoCRh,	1.5 (N = 1)	0.0+, 1.5+, 1.6, 11.4	0.0+, 1.5+, 1.5, 1.6,

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months		(N = 4)	11.4 (N = 5)
<i>Source: FDA Analysis. + denotes a censoring observation, i.e., no relapse, progression or death by the data cutoff date. NE denotes not estimable. NE = not estimable.</i>			

For the 24 participants who achieved a CR or CRh, the median time to first response was 2.7 months (range: 0.9 to 15 months), and 21 (88%) participants did so within 6 months of initiating the study treatment. The majority of these participants achieved their best response at their first remission; only 1 participant (subject ID ^{(b)(6)} with the longest time to respond) achieved first response of CRh at 15 months prior to best response of CR at 18.7 months of treatment.

The transfusion independence data are summarized in FDA Table 36 for Pooled Efficacy Cohort, with 21.2% of participants achieving transfusion independence, and 26.1% of participants maintaining transfusion independence. These results appeared similar to those in the Phase 2 portion, where the transfusion independence rate was 17/75 (22.7%) and transfusion maintenance rate was 2/17 (11.8%). These low rates may be explained in part by the short duration of treatment (median 9.6 weeks). In addition, the population of patients with disease that had a best response of CR + CRh showed much higher transfusion independence and maintenance rates than those whose disease achieved lesser or no response.

FDA Table 36. Summary of Transfusion Dependence and Independence at Baseline and Post Baseline

	Post-baseline Transfusion Independence n (%), 95% CI
Pooled Efficacy Cohort (N = 112)	
Baseline Transfusion Dependent (n = 66)	14 (21.2%, [12.1%, 33.0%])
Baseline Transfusion Independent (n = 46)	12 (26.1%, [14.3%, 41.1%])
Participants who achieved CR + CRh (N = 24)	
Baseline Transfusion Dependent (n = 13)	11 (84.6%, [54.6%, 98.1%])
Baseline Transfusion Independent (n = 11)	9 (81.8%, [48.2%, 97.7%])
Participants who did not achieve CR + CRh (N = 88)	
Baseline Transfusion Dependent (n = 53)	3 (5.7%, [1.2%, 15.7%])
Baseline Transfusion Independent (n = 35)	3 (8.6%, [1.8%, 23.1%])
<i>Source: FDA Analysis</i>	

Clinical TL Comment: Of particular concern is the lack of substantive achievement of transfusion independence or maintenance of transfusion independence in participants not achieving a disease status CR or CRh. This suggests that the benefit of ziftomenib is limited to participants who achieve disease control with ziftomenib monotherapy.

The median OS was estimated similarly in the Pooled Efficacy Cohort and its Phase 2 subset: 6.1 (95% CI: 3.8, 8.6) and 6.6 (95% CI: 3.6, 8.6) months, respectively. OS is not interpretable in a single-arm trial, so OS was not considered further, except to observe that this appears to be a numerical improvement in OS compared to historical controls, as described by the Applicant

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above.

Four (3.6%) of 112 participants underwent HSCT following the study treatment, and three resumed ziftomenib after transplant. Given that the study was not designed to evaluate the benefit and risk profile of such post HSCT resumption, these results were exploratory and not included in the USPI.

Dose/Dose Response

Data:

The relationship between ziftomenib steady-state exposure and 4 different combinations of efficacy endpoints was assessed in efficacy E-R analysis, as discussed in Sections 6.2.1 and 6.2.2.1. There were no statistically significant correlations between steady state AUC, C_{max} or C_{trough} and any efficacy endpoint. Based on these analyses it can be concluded that there is no exposure-efficacy relationship across the observed exposure range in patients with *NPM1*-m AML.

The Applicant's Position:

The integration of ziftomenib exposure-response findings for both efficacy and safety support the recommended dose of 600 mg QD dose of ziftomenib as the optimal regimen, maximizing efficacy in patients with *NPM1*-m R/R AML while maintaining a favorable safety profile.

The FDA's Assessment:

Please see Section 6 for a description of the exposure/response analyses.

Durability of Response

Data:

The 21.7% CR/CRh rate was achieved in a median time to CR/CRh response of 2.8 months (95% CI: 1.0, 15.0) and a subsequent median duration of CR/CRh response of 3.7 months (95% CI: 1.9 to 7.4) for a median period of disease control of greater than 6 months for CR/CRh (refer to Applicant Table 9 and Applicant Table 10). Due to the potential for instability of KM estimates at lower sample sizes or significant censoring, an ad hoc restricted mean for each of the response durations was performed in accordance with FDA guidance. The restricted mean duration of CR/CRh response was 4.7 months (95% CI: 2.9, 6.5), validating the aforementioned duration of response estimates as clinically meaningful.

The positive CR/CRh results are supported by a clinically meaningful median composite complete remission (CRc) rate (26.1% [95% CI: 17.5, 36.3]), which includes patients achieving CR/CRh and CR with incomplete hematologic recovery (CRi). The median time to CRc response was 2.8 (95% CI: 0.8, 4.6) months and a median CRc duration of 4.6 (95% CI: 2.8, 11.4)

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months. The time to and durability of CRc response encompassed a 7.3-month period of patients receiving a durable clinical benefit in this heavily pretreated and deeply refractory population beyond those achieving CR/CRh alone. The probability of maintaining a CRc response at 6 months was 37.2% (95% CI: 15.5, 59.1). Additional analysis of CRc responses using a restricted mean DOR truncated at the time when at least 10% of patients remained at risk resulted in a restricted mean DOR of 5.7 months (95% CI: 3.8, 7.6), validating the CRc responses reported above.

In addition, ORR provides critical context for the durability of response associated with ziftomenib treatment. In the Phase 2 mITT population, ORR was achieved in 30 (32.6% [95% CI: 23.2, 43.2]) patients and a duration of overall response of 4.6 (95% CI: 2.8, 7.4) months, with similar proportions of patients achieving ORR and durations of ORR in the supportive Phase 1b EAS population, as described in 8.1.2. Median OS was 6.6 months in patients treated with ziftomenib, with 12-month and 18-month probabilities of maintaining this response of 30.6% and 28.0%, respectively.

The Applicant's Position:

The durable CR/CRh rate, supported by other durable measures of clinical benefit (CRc, ORR) represent a clinically meaningful treatment effect and substantial improvement over historically available data in this deeply relapsed, refractory population otherwise relegated to cytotoxic treatment options in the palliative setting.

The FDA's Assessment:

Among the 24 participants who achieved CR or CRh on treatment, 17 participants had disease that either progressed or relapsed, 1 died, 1 started subsequent anti-cancer therapy and relapsed after this initiation, 2 discontinued treatment and withdrew from study without disease progression or relapse, and 3 remained in remission at the time of the data cutoff date of 21 March 2025. Among the 3 participants who had ongoing response, none received HSCT after the ziftomenib treatment. The review team notes that comparison to historical controls is difficult due to potential confounding variables, including differences in patient and disease characteristics. As such, any comparison to data outside of the trial should be interpreted with caution.

Persistence of Effect

The Applicant's Position:

Data were not analyzed to evaluate persistence of effect.

The FDA's Assessment:

See the above sections regarding durability of responses and transfusion independence.

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Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant’s Position:

No secondary or exploratory COA (PRO) endpoints were assessed.

The FDA’s Assessment:

The FDA agrees with the Applicant’s position.

Additional Analyses Conducted on the Individual Trial

The Applicant’s Position:

No additional analyses were performed.

The FDA’s Assessment:

The FDA agrees with the Applicant’s position.

8.2. Integrated Review of Effectiveness

8.2.1. Assessment of Efficacy Across Trials

The Applicant’s Position:

Clinical efficacy was assessed using data and analysis from Study KO-MEN-001, there were no additional trials for the assessment of clinical efficacy that were integrated. The data from KO-MEN-001 Phase 2 is a single adequate, well-controlled trial that provides the primary efficacy analysis to support the proposed indication. The Phase 1b results provide supportive evidence. The results for Phase 1b are presented alongside the primary analysis population in Section 8.1.2.

The FDA’s Assessment:

Methods

The Applicant proposed an indication “for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an *NPM1* mutation,” with a dose of ziftomenib 600 mg PO daily.

Issues with the clinical development program:

The clinical development program included one multiple-cohort, single-arm, Phase 1-2 trial of ziftomenib monotherapy (KO-MEN-001) in adult patients ≥ 18 years of age with relapsed or refractory acute myeloid leukemia with an *NPM1* mutation by local testing. The Phase 1a portion was an open-label, dose-escalation study with 7 cohorts and included multiple genetic subtypes of R/R acute leukemia. The Phase 1b portion treated participants with R/R *NPM1*-m AML with 200 mg daily (n=17) or 600 mg daily (n=36) of ziftomenib. The Phase 2 portion included a

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single cohort of participants treated with ziftomenib 600 mg daily, designed to target a CR + CRh rate of 25% and exclude a 12% null rate.

- A major limitation in the developmental program is that only one adequate and well-controlled study was conducted to support this application, and the study was a single-arm, non-randomized study. In general, for a single pivotal study to support an NDA, the trial should be well-designed, well-conducted, and provide statistically persuasive efficacy findings that would make a second study ethically or practically impossible to perform. In addition, additional confirmatory evidence should be provided. The Applicant proposed to use the Phase 1b cohort treated at the RP2D as the supporting evidence of effectiveness in addition to the Phase 2 pivotal cohort. However, the final adjudicated responses did not exclude the 12% null rate from the pivotal cohort. As such, the labeled population includes the Pooled Efficacy Cohort of Phase 1b + Phase 2.

Issues with the pivotal trial:

The review team identified several issues with the design and conduct of the trial:

- The protocol and SAP did not specify a window between the marrow sampling and the CBC for remission assessment. This complicated the independent response adjudication based on the raw data. For the adjudication process, the FDA used a window of (-7, +14) days in addition to with clinical judgement. While the results submitted by the Applicant for the Phase 2 cohort excluded the benchmark rate of 12%, the adjudicated results of the Phase 2 cohort did not. This raises questions about the robustness of the results.
- Although the CR + CRh rate in the Phase 2 patients excluded the null hypothesis of 12% based on the Applicant's assessments, it did not based on the FDA's adjudication. The FDA also evaluated this in the Pooled Efficacy Cohort by pooling the Phase 1 patients given two phases had the same eligibility criteria and two phases of patients had similar baseline characteristic. This differed from what was specified in the SAP but provided a more comprehensive experience. The efficacy results from the Pooled Efficacy Cohort appear to confirm the initial inference based on the Applicant's assessments for Phase 2 patients only. The FDA evaluated the impact of borrowing from Phase 1 data in sensitivity analyses, concluding that the inference was generally similar even when the Phase 1 data were only partially used for pooling.
- Remission is generally delayed in onset for other molecularly targeted agents for treatment of AML compared to traditional cytotoxic therapy. For the Pooled Efficacy Cohort in Study KO-MEN-001, the median time on treatment was only 9.6 weeks. How this short follow-up time affected observation of the efficacy endpoints needs to be considered.
- Of note is the low proportion of patients achieving CR + CRh, the low rate of conversion to transfusion independence and the low rate of maintenance of transfusion independence. These observations may be explained in part by the short duration of

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treatment. However, given the limitations of the benefit of ziftomenib in the proposed patient population, the proposed broad indication statement, including all adult patients with R/R *NPM1*-m AML, was not representative of the benefit-risk assessment of ziftomenib. The review team elected to proceed with a narrower indication statement, with the indicated patient population: adult patients with R/R AML with a susceptible *NPM1* mutation who have no satisfactory alternative treatment options.

- The benefit and risk profile of post-transplant resumption of treatment was not possible to evaluate with the study design. Therefore, (b) (4)

posttransplant resumption will not be included in dosing instructions in the USPI.

Clinical Benefit Endpoint(s)

For nonmyelosuppressive drugs given in settings without curative intent, the FDA has accepted durable CR + CRh for regulatory decision making, with adequate blood count recovery and transfusion independence as corroborating evidence. Ziftomenib is considered a nonmyelosuppressive agent (see Section 8.3). The KO-MEN-001 SAP specified CR + CRh rate as the primary efficacy endpoint. Secondary endpoints included duration of response and achievement of transfusion-independence. The review team established efficacy on the basis of CR + CRh, the duration of CR + CRh, the rate of conversion from transfusion dependence to transfusion independence, and the rate of maintenance of transfusion independence in participants who were independent of transfusions at study enrollment (FDA Table 37).

FDA Table 37. Clinical Benefit and Supporting Endpoints (Pooled Efficacy Cohort)

Endpoint	Result
CR + CRh	24/112 (21.4%; 95% CI: 14.2%, 30.2%)
CR	19/112 (17.0%; 95% CI: 10.5%, 25.2%)
CRh	5/112 (4.5%; 95% CI: 1.5%, 10.1%)
Median time to CR + CRh	2.7 (range: 0.9 to 15) months
Median duration of CR + CRh	5.0 (95% CI: 1.9, 8.1) months
Conversion from TD to TI-56	14/66 (21.2%; 95% CI: 12.1%, 33.0%)
Maintenance of TI	12/46 (26.1%; 95% CI: 14.3%, 41.1%)

Source: FDA analysis

Subpopulations

In addition, subgroup analyses by demographic characteristics and baseline disease showed that the treatment effect was observed across all subgroups (See FDA Table 34). These data, taken together with the nonclinical proof of concept data, provide substantial evidence of effectiveness of ziftomenib for treatment of R/R AML with an *NPM1* mutation in adult patients. The low CR + CRh rate and the low rate of conversion transfusion independence warrant careful

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consideration of the risk-benefit assessment.

Supporting Endpoints

See Section 8.1.2 for the analyses of supporting endpoints, including time to response, achievement of transfusion independence (red blood cell and platelet), and overall survival (OS). The results for time to response and conversion to TI are discussed above. As OS is not interpretable in a single-arm trial, it is not considered further here.

Dose/Dose Response

Assessment of monotherapy dose response is challenging due to the limited number of participants with *NPM1*-m AML treated at doses other than the recommended dosage of 600 mg daily during the dose escalation phase of KO-MEN-001. Only 8 participants with *NPM1*-m AML were treated at other doses: 6 at 200 mg daily, 1 at 400 mg daily, and 1 at 800 mg daily. Of these 8 patients, only one (1/6, 17%) participant treated at 200 mg daily was reported to have had a response of CR. Given the small number of participants treated at this dosage, it is unclear if this is the true rate of response at the 200 mg daily dosage or if it represents an unexpected response as this lower dose. It is interesting to note that during the dose escalation phase of development, more participants were enrolled with *KMT2A*-r acute leukemia at alternative dose levels, which ranged from 50 to 1000 mg daily. Of the two dose levels with the highest enrollment of participants with *KMT2A*-r AL, the Applicant saw no responses at the 200 mg dose level (0/14, 0%) and 2 responses (2/18, 11%) in those treated at the 600 mg dose level, suggesting a dose response for ziftomenib in this population.

Additional Efficacy Considerations

Study KO-MEN-001 allowed patients to resume treatment of ziftomenib after transplantation if the following conditions were met:

- Between 30 and 120 days post-HSCT.
- Successful hematopoietic recovery as demonstrated by ANC $\geq$ 0.5 Gi/L and platelets $\geq$ 20 Gi/L without transfusions.
- All non-hematologic transplant AEs be $<$ grade 2.
- Must not have active GVHD.
- Maximum of 0.5 mg/kg of prednisone equivalent.
- Permitted to be on stable doses of calcineurin inhibitors.
- AML in remission.

The FDA noted that only 3 patients resumed ziftomenib treatment after HSCT. Additionally, the benefit and risk profile of such posttransplant resumption of treatment was not possible to

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evaluate with the study design. Therefore, [REDACTED] posttransplant resumption will not be included in dosing instructions in the USPI. (b) (4)

Lastly, the question of what data would support SEE required additional discussion, as the majority of efficacy analyses utilized the Pooled Efficacy Cohort. Ultimately, the similar response rates, duration of response, and achievement of transfusion independence in the Phase 1b and Phase 2 cohorts led the review team to consider these cohorts separately, with the Phase 2 cohort providing the primary support as one well-controlled study, and the Phase 1b cohort providing additional confirmatory evidence. The FDA also considered the observation of activity in a population with other genetic variants associated with HOXA overexpression (i.e., *KMT2A-r* AML), lack of efficacy in participants with AML not having genetic variants associated with HOXA overexpression (other genetic variants, 1/16 responses, 6% response rate), the *in vitro* cytotoxic effect of prolonged ziftomenib exposure on AML cell lines (Section 5.3), and tumor growth inhibition in xenograft models (Section 5.3).

8.2.2. Integrated Assessment of Effectiveness

The Applicant's Position:

Clinical efficacy was assessed using data and analysis from Study KO-MEN-001, there were no additional trials for the assessment of clinical efficacy that were integrated. The primary efficacy endpoint for Phase 2 was the CR/CRh rate. CR/CRh rate is an accepted binary efficacy endpoint commonly used to demonstrate direct clinical benefit to support full approval of treatments for AML in the palliative setting, per FDA guidance for industry (Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment; 2022). This approach, with demonstration of durability and transfusion independence, was used previously with FDA-approved targeted inhibitors in R/R acute leukemia (eg, revumenib, olutasidenib, ivosidenib, enasidenib, gilteritinib).

The KO-MEN-001 Phase 2 cohort met the primary endpoint with statistical significance, demonstrating a CR/CRh rate of 21.7% with a narrow CI (95% CI: 13.8, 31.6; $p=0.0058$). The CR/CRh rate compared favorably to the conservative historical control of 12%. The median time for patients to achieve CR/CRh was 2.8 months (95% CI: 1.0, 15.0) after treatment initiation, which is consistent with the mechanism of action of a differentiating agent. Responses to treatment were durable with a median CR/CRh duration of response of 3.7 months (95% CI: 1.0, 15.0 months). These results suggest a median period of disease control for CR/CRh exceeding 6 months. The restricted mean DOR for CR/CRh when truncated at the time when at least 10% of patients remained at risk was 4.7 months (95% CI: 2.9, 6.5), validating the median DOR estimate. The probability of having a CR/CRh response with a duration of 6 months was 33.5% (95% CI: 11.2, 57.8). Furthermore, two-thirds of responders achieved CR (14.1%), which compares favorably to the control arm of low-intensity salvage chemotherapy in the ADMIRAL

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study in which the CR rates were only 2% and CRc rates were 4% (Perl et al, 2019). The median time to CR response was 2.3 months (95% CI: 0.9, 7.4) with a median duration of CR of 5.6 months (95% CI: 0.6, 8.1) for a median period of disease control of approximately 8 months in this population. In patients who achieved a CR/CRh, the responses were deep as evidenced by a majority (64.3% [95% CI: 35.1, 87.2]) of responding patients achieving MRD- on local readings as well as clinically meaningful rates of CRc (26.1%) and ORR (32.6%).

Improvements in platelet count are associated with decreased transfusion burden and lower risk of related complications. Among the 82 patients who were dependent on RBC and/or platelet transfusions at baseline, 16 (19.5%) patients experienced conversion from TD to transfusion independent (TI) for both RBC and platelets and 2 of 10 (20.0%) patients maintained their TI (TI to TI) for a 56-day postbaseline period. Ziftomenib has been demonstrated to be a nontoxic and nonmyelosuppressive treatment, rendering TI an applicable measure of direct clinical benefit corroborating the clinical endpoint of CR/CRh.

The data from KO-MEN-001 Phase 2 provide is a single adequate, well-controlled trial that provides the primary efficacy analysis to support the proposed indication to support the proposed indication, with Phase 1b providing supportive evidence. The results for Phase 1b are presented with the primary analysis population in Section 8.1.2. The totality of efficacy data provide additional supportive evidence of a clinically meaningful and durable improvement in disease control with ziftomenib in R/R *NPM1*-m AML, which remains difficult to treat this setting and for which no FDA-approved targeted therapies exist.

The FDA's Assessment:

The efficacy of ziftomenib was established based on the results of the Phase 2 pivotal cohort in Study KO-MEN-001 in adult participants with R/R AML with an *NPM1* mutation, with confirmatory data from the Phase 1b cohort of participants with *NPM1*-m AML treated at the recommended dosage of 600 mg daily. The demographics of the study population were consistent with those of the US population with *NPM1*-m AML, and the results were considered generalizable to the US population (see Section 8.1.1).

In Study KO-MEN-001, eligible participants who received ziftomenib at the recommended dosage had a CR/CRh rate of 21.4% (95% CI: 14.2%, 30.2%) in the Pooled Efficacy Cohort and 18.5% (95% CI: 11.1%, 27.9%) in its Phase 2 subset (FDA Table 37). The median duration of response was 5.0 (95% CI: 1.9, 8.1) months, and the median time to response was 2.7 (range: 0.9 to 15) months in the Pooled Efficacy Cohort. The rate of conversion to transfusion independence was 21.2% (95% CI: 12.1%, 33.0%) and transfusion maintenance rate was 26.1% (95% CI: 14.3%, 41.1%) in the Pooled Efficacy Cohort.

The relatively low CR/CRh rate, low TI rate, and short follow-up limiting assessment of durability leads to some uncertainty about clinical benefit. However, the results from the Phase 2 efficacy cohort of Study KO-MEN-001 and the additional confirmatory data from the Phase 1b portion of KO-MEN-001 are considered substantial evidence of effectiveness of ziftomenib for

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the treatment of R/R AML with a susceptible *NPM1* mutation who have no satisfactory alternative treatment options.

8.2.3. Approach to Substantial Evidence of Effectiveness

1. Verbatim indication (*enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response*):

[Click here to enter the verbatim indication.](#)

2. SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)

- a. Adequate and well-controlled clinical investigation(s):

- i. Two or more adequate and well-controlled clinical investigations, **OR**
- ii. One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

- b. One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}

OR

- c. Evidence that supported SEE from a prior approval (*e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch*)²

3. Complete response, if applicable

- a. SEE was established
- b. SEE was not established (*if checked, omit item 2*)

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

³ *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (2023)]

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8.3. Review of Safety

THE APPLICANT'S POSITION

The pivotal study, KO-MEN-001 (main study), was the primary source of data for the evaluation of the safety of 600 mg QD of ziftomenib as a monotherapy for the treatment of patients with R/R *NPM1*-m AML. The primary safety population included all patients with a confirmed *NPM1* mutation who received 600 mg QD, including the 92 patients in Phase 2 and 20 patients in Phase 1b for a total of 112 patients.

Additional supportive sources of safety data summarized within the application include other ongoing clinical studies of ziftomenib. The KO-MEN-001 sub-studies are evaluating drug-drug interactions in non-*NPM1*-m AML (sub-studies 1 and 2) or ziftomenib activity in ALL (sub-study 3), and Studies KO-MEN-007 and KO-MEN-008 evaluate ziftomenib in combination with standard-of-care regimens (eg, venetoclax, azacitidine, intensive and low-dose chemotherapy, and gilteritinib). As these data do not directly inform the proposed indication of patients with R/R *NPM1*-m AML due to the inherent heterogeneity of combination agents, molecular types and study populations, summary-level data are presented in the application for a comprehensive package without integration. For studies evaluating the combination of ziftomenib with standard-of-care regimens (eg, KO-MEN-007 and KO-MEN-008), safety data will be summarized for each individual cohort within each study.

There were also two completed (KO-MEN-003, KO-MEN-005) and one terminated (KO-MEN-006) PK studies in healthy volunteers. Safety data from these studies are presented individually in the respective CSRs and were not included in the ISS.

8.3.1. Safety Review Approach

Data:

The pivotal study, Study KO-MEN-001, was the primary source for the evaluation of the safety of ziftomenib 600 mg QD as monotherapy for the treatment of patients with R/R *NPM1*-m AML (N=112).

In the narrative portion of the ISS, safety information presentation was organized into 3 population groups, as agreed at the Type C Safety Analysis Strategy meeting, with the focus being on the population supporting the target indication and all non-indication analyses were presented in the NDA for completeness but considered supplementary (Applicant Table 14).

Applicant Table 14: Applicant – Predefined Safety Populations

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Safety Analysis Population	Description	Contributing Studies
Safety-1 (n=112)	R/R <i>NPM1</i> -m AML dosed at 600 mg QD (<u>target indication</u>)	KO-MEN-001: Phase 1 and Phase 2
Safety-2 (n=186)	All ziftomenib monotherapy in R/R AML: <i>NPM1</i>-m, <i>KMT2A</i>-r, and other genetic forms of AML - Doses ranging from 50 to 1000 mg QD - Pooling: Data presented by molecular type and dose level	KO-MEN-001: Phase 1, Phase 2, SS1, and SS2
Safety-3 (n=173)	All other ziftomenib in hematologic malignancies: - ALL - AML combinations in intensive chemotherapy eligible patients (1L and R/R) - AML combinations in nonintensive chemotherapy patients (1L and R/R) No pooling of data from different studies planned. Data presented by study/cohort/ molecular type	KO-MEN-001: SS3 (ALL) KO-MEN-007 KO-MEN-008

The Applicant's Position:

Pivotal Study KO-MEN-001 (main study) will be the primary source for the evaluation of the safety of ziftomenib for the treatment of patients with R/R *NPM1*-m AML in this NDA. Safety data from other supportive studies, including doses of ziftomenib other than 600 mg QD, non-*NPM1*-m molecular types of AML, or combination regimens do not directly inform the safety profile of the proposed indication.

8.3.2. Review of the Safety Database

Overall Exposure

Data:

Overall, the median number of doses received was 61.0 (range: 2 to 509). The median duration of exposure was 9.64 weeks (range: 0.3 to 72.9 weeks). The median cumulative dose was 36,600.0 mg (range: 1200 to 269,600 mg), the median dose intensity was 600.0 mg/day (range: 217.0 to 633.0 mg/day), and the median RDI was 100.0% (range: 36.2% to 105.5%; Applicant Table 15).

Applicant Table 15: Applicant - Ziftomenib Exposure Summary

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	Part 1b EAS 600 mg QD (N=20)	Phase 2 mITT 600 mg QD (N=92)	600 mg QD Monotherapy NPM1-m R/R AML (N=112)
Number of doses received			
N	20	92	112
Mean (SD)	103.4 (85.83)	82.2 (76.74)	86.0 (78.46)
Median	71.5	60.0	61.0
Min, max	14, 298	2, 509	2, 509
Q1, Q3	48.0, 120.5	28.0, 114.5	28.0, 114.5
Duration of exposure, weeks			
N	20	92	112
Mean (SD)	14.96 (12.282)	12.87 (11.728)	13.25 (11.800)
Median	10.21	9.57	
Min, max	2, 42.6	0.3, 72.9	0.3, 72.9
Q1, Q3	6.86, 18.36	5.07, 18.86	5.29, 18.86
Cumulative dose, mg			
N	20	92	112
Mean (SD)	60,910.0 (52,555.31)	47,937.0 (43,574.49)	50,253.6 (45,324.56)
Median	39600.0	36000.0	36600.0
Min, max	8400, 178800	1200, 269600	1200, 269600
Q1, Q3	26500.0, 72300.0	16500.0, 62700.0	16800.0, 63600.0
Dose intensity, mg/day			
N	20	92	112
Mean (SD)	580.54 (74.108)	542.19 (91.909)	549.04 (89.905)
Median	600.00	594.17	600.00
Min, max	276.2, 633.0	217.0, 600	217.0, 633.0
Q1, Q3	600.00, 600.00	507.14, 600.00	528.49, 600.00
Relative dose intensity, %			
N	20	92	112
Mean (SD)	96.76 (12.351)	90.37 (15.318)	91.51 (14.984)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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	Part 1b EAS 600 mg QD (N=20)	Phase 2 mITT 600 mg QD (N=92)	600 mg QD Monotherapy NPM1-m R/R AML (N=112)
Median	100.00	99.03	100.00
Min, max	46.0, 105.5	36.2, 100	36.2, 105.5
Q1, Q3	100.00, 100.00	84.52, 100.00	88.08, 100.00

Source: KO MEN 001 CSR, Table 14.2.11.1.4

The Applicant's Position:

The 600 mg QD Monotherapy NPM1-m R/R AML Safety Analysis Population includes R/R AML patients with locally confirmed NPM1-m enrolled in KO-MEN-001 main study, which is composed of the Part 1b Efficacy Analysis Set (EAS) and Phase 2 modified Intent-to-Treat Analysis Set, who have received an initial dose of 600 mg QD of ziftomenib. The exposure to ziftomenib observed in the populations studied in KO-MEN-001 is appropriate for the proposed indication population. No clinically relevant differences in exposure were observed in the other supportive patient populations presented in Module 2.7.4/ISS.

Relevant characteristics of the safety population:

Data:

Patient demographics were previously presented in Section 8.1.2. Overall, the median age of patients was 69.0 years (range: 22 to 86 years) and 56.3% of patients were female. Most patients (56.3%) had an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 1. Patients had median baseline bone marrow blasts of 44.0% (range: 0.5% to 98%). Most patients had de novo AML (95 patients [84.8%]). Patients had median prior lines of therapy of 2.0 (range: 1 to 7).

The Applicant's Position:

The demographics of the population are indicative of the population of patients for the proposed indication. The supportive Phase 1b population patient demographics were similar to those seen in patients in Phase 2, with any numerical differences being not clinically relevant.

Adequacy of the safety database:

The Applicant's Position:

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The safety analysis strategy was agreed in the May 2024 Type C written responses. The content of this clinical package was discussed and considered adequate at the February 2025 Pre-NDA meeting, as was the content and timing of the safety update.

Phase 2 was designed for registrational intent, with a final total enrollment of 92 patients, to ensure a robust safety database for patients at the intended registrational dose and population of 600 mg in R/R *NPM1*-m AML patients and to assess efficacy. The data cutoff of 28 Oct 2024 provides a minimum of 6 cycles of follow-up from the start of treatment for the prespecified Phase 2 population. Patients with R/R *NPM1*-m AML and treated with ziftomenib 600 mg QD were enrolled with the same eligibility criteria, treated with the same protocol, and demonstrated consistent demographics, safety, and efficacy as the Phase 2 population. The addition of the 20 Phase 1b patients to the primary analysis population of 92 Phase 2 patients, for a total of 112 patients with R/R *NPM1*-m AML treated at the proposed ziftomenib dose of 600 mg QD, provides an adequate sample to assess the safety of ziftomenib.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No concerns have been identified in the quality and integrity of the submitted datasets and individual case narratives.

Categorization of Adverse Event

The Applicant's Position:

All adverse events (AEs) recorded in the electronic case report forms were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 27.0) and graded using Common Terminology Criteria for Adverse Events (CTCAE; version 5.0).

TEAEs were summarized for the initial treatment-emergent period, the maintenance treatment-emergent period after on-treatment HSCT (only for those who had maintenance ziftomenib treatment after HSCT), and the maintenance treatment-emergent period without HSCT (only for those who had maintenance ziftomenib treatment without HSCT), separately. Patient incidence of TEAEs was tabulated by system organ class (SOC) and preferred term (PT). Selected TEAEs were tabulated by PT in descending order of frequency. Similar summaries were repeated for AEs of special interest of differentiation syndrome and tumor lysis syndrome.

Routine Clinical Tests

The Applicant's Position:

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Clinical laboratory tests were conducted at a local laboratory and were reasonable and adequate for the indicated population. The specific tests that were done are listed below:

- Hematology: complete blood count including manual differential
- Chemistry: glucose, sodium, potassium, calcium, creatinine, AST, ALT, ALP, lactate dehydrogenase, total bilirubin, urea and/or blood urea nitrogen, cystatin C (sub-studies 1-4 only), total protein, uric acid, albumin and phosphorus
- Urinalysis: pH, glucose, erythrocytes, leukocytes, protein, and nitrite
- Coagulation: fibrinogen, D-dimer, prothrombin time, international normalized ratio, activated partial thromboplastin time, and peripheral blood smear for microangiopathic hemolytic anemia. In instances where activated partial thromboplastin time was not available, partial thromboplastin time may have been performed.
- Pregnancy: Serum test at screening; urine or serum test at all other timepoints
- Inflammatory Markers: ferritin, C-reactive protein plasma levels, and erythrocyte sedimentation rate

8.3.4. Safety Results

Deaths

Data:

Overall, of the 71 (63.4%) patients who discontinued the study due to death, 27 (24.1%) patients who experienced a TEAE that lead to death during Study KO MEN 001 in the 600 mg QD monotherapy *NPM1*-m R/R AML safety population (N=112), with the most common events being sepsis (5 patients [4.5%]), pneumonia (3 patients [2.7%]), respiratory failure (3 patients [2.7%]), respiratory distress and cardiac arrest (2 patients [1.8%] each). No TEAEs leading to death were considered related to ziftomenib treatment. All other events were single reports.

The Applicant's Position:

R/R *NPM1*-m AML is a serious, progressive disease that is nearly universally fatal. Due to events attributable to underlying disease progression, on-study deaths are expected in this population. Overall in the indication population, approximately 25% of subjects reported a TEAE that lead to death with the main PTs being sepsis, pneumonia, and respiratory failure. Notably, no cases of differentiation syndrome led to death in this population of patients with R/R *NPM1*-m AML. None of these TEAEs leading to death were considered related to ziftomenib treatment.

Serious Adverse Events

Data:

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A total 89 patients (79.5%) in the 600 mg QD monotherapy *NPM1*-m R/R AML population experienced at least 1 serious adverse event (SAE) during ziftomenib treatment (Applicant Table 16), with the events of febrile neutropenia, DS, sepsis, and pneumonia being the most commonly reported. In this population, 30 patients (26.8%) experienced an SAE that was considered related to ziftomenib treatment, with the majority of these being DS (16 patients [14.3%]) and diarrhea, dyspnea, febrile neutropenia, and white blood cell count increased (each in 2 patients [1.8%]).

Applicant Table 16: Applicant - Serious Adverse Events by System Organ Class and Preferred Term in $\geq 5\%$ of Patients Overall

	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy <i>NPM1</i> -m R/R AML (N=112) n (%)
Patients with at least 1 SAE	16 (80.0)	73 (79.3)	89 (79.5)
Infections and infestations	7 (35.0)	45 (48.9)	52 (46.4)
Sepsis	0	13 (14.1)	13 (11.6)
Pneumonia	2 (10.0)	10 (10.9)	12 (10.7)
Blood and lymphatic system disorders	1 (5.0)	27 (29.3)	28 (25.0)
Febrile neutropenia	1 (5.0)	19 (20.7)	20 (17.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (10.0)	14 (15.2)	16 (14.3)
Differentiation syndrome	2 (10.0)	14 (15.2)	16 (14.3)

Source: *KO MEN 001 CSR, Table 14.3.1.2.3.4*

The Applicant's Position:

R/R *NPM1*-m AML is a serious, progressive disease that is nearly universally fatal. Considering events attributable to the underlying progressive disease, the incidence of SAEs reported in the 600 mg QD monotherapy *NPM1*-m R/R AML population is expected in this patient population. Most patients reported at least 1 SAE with key events of febrile neutropenia, differentiation syndrome, sepsis, and pneumonia. There were 30 (26.8%) patients who experienced an SAE deemed related to ziftomenib treatment with the only related events reported in $\geq 5\%$ of patients being differentiation syndrome, which was demonstrated to be manageable. Discussion on DS are provided in Section 8.3.5.

Discontinuations, Interruptions, or Dose Reductions Due to Adverse Effects

Data:

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In the 600 mg QD monotherapy *NPM1*-m R/R AML population, 24 patients (21.4%) experienced at least 1 TEAE that lead to ziftomenib discontinuation, with the events of sepsis (4 patients [3.6%]) and pneumonia (3 patients [2.7%]) being the most common events (Applicant Table 17). There were 3 patients (2.7%) who experienced a ziftomenib-related TEAE that led to treatment discontinuation, with the events of DS (2 patients [1.8%]) and vomiting (1 patient [0.9%]).

A total of 60 patients (53.6%) experienced a TEAE that lead to a ziftomenib dose interruption, with the most common events being DS (15 patients [13.4%]), sepsis (9 patients [8.0%]), and febrile neutropenia (6 patients [5.4%]) (Table 18). There were 34 patients (30.4%) who experienced a ziftomenib-related TEAE that led to a ziftomenib dose interruption, with the most common PT of DS (15 patients [13.4%]). All other reports of ziftomenib-related TEAEs leading to dose interruption in >1 patient were white blood cell count increased (3 patients [2.7%]) and leukocytosis, diarrhea, and pruritus (2 patients [1.8%] each). A further discussion on DS and the DS mitigation guidance are provided in Section 8.3.5.

There were few patients (4 [3.6%]) who experienced a TEAE that lead to ziftomenib dose reduction in the 600 mg QD monotherapy *NPM1*-m R/R AML population, all of which were single reports of the PTs of neutropenia, pericarditis, ECG QT prolonged, and DS. The TEAEs of neutropenia, ECG QT prolonged, and DS were assessed as related to ziftomenib.

Applicant Table 17: Applicant - TEAEs Leading to Ziftomenib Discontinuation, Interruption, or Dose Reduction by Preferred Term in >1 Patient

	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy <i>NPM1</i> -m R/R AML n (%)
Patients with at least 1 TEAE leading to ziftomenib discontinuation			24 (21.4)
Sepsis	0	4 (4.3)	4 (3.6)
Pneumonia	0	3 (3.3)	3 (2.7)
Septic shock	1 (5.0)	1 (1.1)	2 (1.8)
Cardiac arrest	0	2 (2.2)	2 (1.8)
Differentiation syndrome	0	2 (2.2)	2 (1.8)
Patients with at least 1 TEAE leading to ziftomenib dose interruption			60 (53.6)
Differentiation syndrome	1 (5.0)	14 (15.2)	15 (13.4)
Sepsis	0	9 (9.8)	9 (8.0)
Febrile neutropenia	0	6 (6.5)	6 (5.4)

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	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy NPM1-m R/R AML n (%)
Pyrexia	1 (5.0)	4 (4.3)	5 (4.5)
ECG QT prolonged	0	4 (4.3)	4 (3.6)
Pneumonia	1 (5.0)	3 (3.3)	4 (3.6)
Escherichia sepsis	0	3 (3.3)	3 (2.7)
Septic shock	1 (5.0)	1 (1.1)	2 (1.8)
Leukocytosis	1 (5.0)	1 (1.1)	2 (1.8)
Neutropenia			1 (0.9)
White blood cell count increased	0	3 (3.3)	3 (2.7)
Diarrhoea	0	2 (2.2)	2 (1.8)
Cholecystitis	0	2 (2.2)	2 (1.8)
Pruritus	0	2 (2.2)	2 (1.8)
Patients with at least 1 TEAE leading to ziftomenib dose Reduction			4 (3.6)
Neutropenia	0	1 (1.1)	1 (0.9)
Pericarditis	1 (5.0)	0	1 (0.9)
Electrocardiogram QT prolonged	0	1 (1.1)	1 (0.9)
Differentiation syndrome	0	1 (1.1)	1 (0.9)

Source: KO-MEN-001 CSR, Table 14.3.1.2.6.4 and Table 14.3.1.2.7.4

The Applicant's Position:

Few patients had a TEAE that led to discontinuation or dose reduction. While differentiation syndrome was the most frequently reported TEAE that led to dose interruption, importantly, these data demonstrate that DS was manageable with the guidance provided in the protocol, consistent with proposed labeling, which instructed treatment interruption upon first suspicion and initiation of systemic corticosteroids, followed by resuming ziftomenib at the same dose level when DS signs or symptoms improved to Grade 2 or lower. Following implementation of this DS management guidance, no additional Grade 4 or 5 events were reported in either genotype. Additional details on DS are provided in Section 8.3.5.

Significant Adverse Events

Data:

209

Version date: March 1, 2024 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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There were 105 (93.8%) patients in the 600 mg QD Monotherapy *NPM1*-m R/R AML population who experienced a TEAE of a CTCAE Grade ≥ 3 (

Applicant Table 18). There were 45 (40.2%) patients who experienced a ziftomenib-related CTCAE Grade ≥ 3 TEAE in the 600 mg QD Monotherapy *NPM1*-m R/R AML population. Notably, the adverse reaction of DS was reported as a $\geq$ Grade 3 TEAE in 15 (13.4%); all cases were Grade 3 with no Grade 4 or 5 events of DS.

Applicant Table 18: Applicant - TEAEs With CTCAE Grade ≥ 3 by Preferred Term in $\geq 5\%$ of Patients

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	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy NPM1-m R/R AML (N=112) n (%)
Patients with at least 1 Grade $\geq$3 TEAE	19 (95.0)	86 (93.5)	105 (93.8)
Febrile neutropenia	1 (5.0)	24 (26.1)	25 (22.3)
Anaemia	5 (25.0)	18 (19.6)	23 (20.5)
Thrombocytopenia	4 (20.0)	18 (19.6)	22 (19.6)
Pneumonia	4 (20.0)	13 (14.1)	17 (15.2)
Differentiation syndrome	1 (5.0)	14 (15.2)	15 (13.4)
Neutropenia	2 (10.0)	13 (14.1)	15 (13.4)
Platelet count decreased	1 (5.0)	14 (15.2)	15 (13.4)
Sepsis	1 (5.0)	13 (14.1)	14 (12.5)
Hypokalaemia	1 (5.0)	12 (13.0)	13 (11.6)
Hyperglycaemia	3 (15.0)	7 (7.6)	10 (8.9)
ECG QT prolonged	0	8 (8.7)	8 (7.1)
White blood cell count decreased	2 (10.0)	5 (5.4)	7 (6.3)
Alanine aminotransferase increased	0	6 (6.5)	6 (5.4)
Fatigue	1 (5.0)	5 (5.4)	6 (5.4)
Hypertension	1 (5.0)	5 (5.4)	6 (5.4)
Hypoxia	1 (5.0)	5 (5.4)	6 (5.4)
Patients with at least 1 ziftomenib-related Grade $\geq$ 3 TEAE	8 (40.0)	37 (40.2)	45 (40.2)
Differentiation syndrome	1 (5.0)	14 (15.2)	15 (13.4)
Anaemia	1 (5.0)	5 (5.4)	6 (5.4)
Neutropenia	0	6 (6.5)	6 (5.4)

Source: Module 2.7.4/ISS, Table 2.7.4.2.2.3.1 and Table 2.7.4.2.2.4.1; KO-MEN-001 CSR, Table 14.3.1.2.12.4

The Applicant's Position:

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A majority of patients experienced at least 1 CTCAE Grade ≥ 3 TEAE primarily related to underlying disease. The most common TEAEs of CTCAE Grade ≥ 3 were febrile neutropenia, anaemia, and thrombocytopenia. Notably, the adverse reaction of DS was reported as a $\geq$ Grade 3 TEAE in 15 (13.4%); all cases were Grade 3 with no Grade 4 or 5 events of DS. A discussion on DS events is presented in Section 8.3.5.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Overall, in the 600 mg QD monotherapy *NPM1*-m R/R AML population, all patients experienced at least 1 TEAE during ziftomenib treatment with the majority of patients experiencing a TEAE with a Grade ≥ 3 (93.8%) and/or a serious TEAE (79.5%). Similarly, most patients (68.8%) experienced at least 1 ziftomenib-related TEAE during treatment in this population (Applicant Table 19).

Applicant Table 19: Applicant - Overview of Treatment-Emergent Adverse Events

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	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy <i>NPM1</i>- m R/R AML (N=112) n (%)
TEAE (all causality)	20 (100)	92 (100)	112 (100)
Ziftomenib-related	13 (65.0)	64 (69.6)	77 (68.8)
Grade ≥ 3 TEAE	19 (95.0)	86 (93.5)	105 (93.8)
Ziftomenib-related	8 (40.0)	37 (40.2)	45 (40.2)
Serious TEAE (all causality)	16 (80.0)	73 (79.3)	89 (79.5)
Ziftomenib-related	6 (30.0)	24 (26.1)	30 (26.8)
TEAE leading to ziftomenib dose reduction	1 (5.0)	3 (3.3)	4 (3.6)
Ziftomenib-related	0	3 (3.3)	3 (2.7)
TEAE leading to ziftomenib dose interruption	9 (45.0)	51 (55.4)	60 (53.6)
Ziftomenib-related	4 (20.0)	30 (32.6)	34 (30.4)
TEAE leading to ziftomenib permanently discontinued	5 (25.0)	19 (20.7)	24 (21.4)
Ziftomenib-related	0	3 (3.3)	3 (2.7)
TEAE leading to death	6 (30.0)	21 (22.8)	27 (24.1)
Ziftomenib-related	0	0	0

Source: *KO-MEN-001 CSR, Table 14.3.1.1.4*

Frequently reported TEAEs were defined as TEAEs of any grade that were reported in $\geq 20\%$ of patients treated with ziftomenib 600 mg QD monotherapy. Of these TEAEs reported by patients in the 600 mg QD monotherapy *NPM1*-m R/R AML population, diarrhea, nausea, hypokalemia, DS, and pruritus were the most common (Applicant Table 20).

Applicant Table 20: Applicant - Treatment-Emergent Adverse Events Reported in $\geq 20\%$ of Patients by Preferred Term

Preferred Term	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy <i>NPM1</i>- m R/R AML (N=112) n (%)
Patients with at least 1 TEAE			112 (100)
Diarrhoea	9 (45.0)	26 (28.3)	35 (31.3)

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Preferred Term	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy <i>NPMI</i> - m R/R AML (N=112) n (%)
Nausea	8 (40.0)	23 (25.0)	31 (27.7)
Hypokalaemia	7 (35.0)	22 (23.9)	29 (25.9)
Differentiation syndrome	4 (20.0)	23 (25.0)	27 (24.1)
Pruritus	5 (25.0)	21 (22.8)	26 (23.2)
Anaemia	5 (25.0)	20 (21.7)	25 (22.3)
Oedema peripheral	2 (10.0)	23 (25.0)	25 (22.3)
Febrile neutropenia	1 (5.0)	24 (26.1)	25 (22.3)
Pneumonia	5 (25.0)	19 (20.7)	24 (21.4)

Source: *KO-MEN-001* CSR, Table 14.3.1.2.1.4; Module 2.7.4/ISS, Table 2.7.4.2.2.1.1

The majority of patients (68.8%) experienced at least 1 ziftomenib-related TEAE in the 600 mg QD monotherapy *NPMI*-m R/R AML population. The most frequently reported TEAEs deemed related to ziftomenib treatment were diarrhea, nausea, hypokalemia, DS, and pruritus (Applicant Table 21). The TEAE of DS was considered an AESI and is further discussed in Section 8.3.5.

Applicant Table 21: Applicant - Treatment-Related Adverse Events Reported in ≥20% of Patients by Preferred Term

Preferred Term	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy <i>NPMI</i> - m R/R AML (N=112) n (%)
Patients with at least 1 TEAE			112 (100)
Diarrhoea	9 (45.0)	26 (28.3)	35 (31.3)
Nausea	8 (40.0)	23 (25.0)	31 (27.7)
Hypokalaemia	7 (35.0)	22 (23.9)	29 (25.9)
Differentiation syndrome	4 (20.0)	23 (25.0)	27 (24.1)
Pruritus	5 (25.0)	21 (22.8)	26 (23.2)
Anaemia	5 (25.0)	20 (21.7)	25 (22.3)
Oedema peripheral	2 (10.0)	23 (25.0)	25 (22.3)
Febrile neutropenia	1 (5.0)	24 (26.1)	25 (22.3)
Pneumonia	5 (25.0)	19 (20.7)	24 (21.4)

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Source: KO-MEN-001 CSR, Table 14.3.1.2.2.4 ; Module 2.7.4/ISS, Table 2.7.4.2.2.1

The Applicant's Position:

The data from the 600 mg QD monotherapy *NPM1*-m R/R AML safety analysis population, supported by the data from the overall integrated safety analysis, demonstrates that the safety profile of continuous 600 mg QD ziftomenib administration for the treatment of *NPM1*-m AML patients meets the criteria of a palliative therapy by being relatively nontoxic and nonmyelosuppressive (FDA, 2022). The reported TEAEs were largely consistent with those associated with underlying AML and consistent with the predictable safety profile of ziftomenib, with ziftomenib displaying similar tolerability to other targeted agents approved for use as palliative therapies.

Laboratory Findings

Data:

Hematology

In patients who continued therapy, increases were observed in mean (SD) hemoglobin levels (93.13 [15.466] g/L), absolute neutrophil count (2.16 [2.792] $\times 10^9/L$), and platelets (93.20 [87.315] $\times 10^9/L$) by Cycle 4 Day 1 that persisted until the EOT or relapse.

Hematology assessments for the 600 mg QD Monotherapy *NPM1*-m R/R AML Safety Analysis Population are detailed in Table 14.3.4.2.4 (summary of hematology tests by visit) and Table 14.3.4.5.4 (shift of CTCAE grade in hematology laboratory tests) of the KO MEN 001 CSR.

Biochemistry

In patients who continued therapy, albumin levels increased, and lactate dehydrogenase levels declined with longer treatment duration, consistent with response and overall clinical improvement.

These changes occurred in the absence of hepatic, renal, or electrolyte changes.

Biochemistry assessments for the 600 mg QD Monotherapy *NPM1*-m R/R AML Safety Analysis Population are detailed in Table 14.3.4.3.4 (summary of biochemistry tests by visit) and Table 14.3.4.6.4 (shift of CTCAE grade in biochemistry laboratory tests) of the KO MEN 001 CSR.

Coagulation

In patients who continued therapy, improvements in D-dimer, international normalized ratio, and activated partial thromboplastin time were observed with prolonged treatment, consistent with response.

Coagulation assessments for the 600 mg QD Monotherapy *NPM1*-m R/R AML Safety Analysis Population are detailed in Table 14.3.4.4.4 (summary of coagulation tests by visit) and Table 14.3.4.7.4 (shift of CTCAE grade in coagulation laboratory tests) of the KO MEN 001.

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The Applicant's Position:

Baseline laboratory values and changes during the course of treatment with ziftomenib were generally expected for the heavily pretreated R/R AML population evaluated and consistent with the course of treatment of the underlying condition.

Vital Signs

Data:

In the 600 mg QD Monotherapy *NPM1*-m R/R AML population, weight change $\geq 10\%$ and increase in DBP by >20 mmHg were also the most common vital sign changes. Weight change $\geq 10\%$ occurred in 21 patients (18.8%) and 19 (17.0%) patients had an increase in their DBP by ≥ 20 mmHg from baseline (Applicant Table 22).

In patients treated with ziftomenib 600 mg QD ziftomenib, the most common ECG abnormalities were reported post-baseline in 17/112 (15.2%), at Cycle 2 Day 1 predose in 6/86 (7.0%), at the 2-hour timepoint in 5/78 (6.4%), and at the 4-hour timepoint in 5/74 (6.8%) (Table 14.3.6.1.4, Listing 16.2.8.5 of the KO MEN-001 CSR).

In Phase 1 Part 1b EAS and Phase 2 mITT, 10 patients (8.9%) had QTcF values exceeding 500 msec. Additionally, 14 patients (12.5%; 5 females and 9 males) experienced QTcF interval changes from baseline >60 msec (Table 128 of the KO-MEN-001 CSR).

Applicant Table 22: Applicant - Summary of Vital Sign Potentially Clinically Significant Abnormalities

Parameter	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy <i>NPM1</i>-m R/R AML (N=112) n (%)
Systolic Blood Pressure			
ABSV <90 mmHg and DFB ≥ 30 mmHg	0	2 (2.2)	2 (1.8)
ABSV ≥ 180 mmHg and IFB ≥ 40 mmHg	0	1 (1.1)	1 (0.9)
Diastolic Blood Pressure			
ABSV <50 mmHg and DFB ≥ 20 mmHg	2 (10.0)	6 (6.5)	8 (7.1)
ABSV ≥ 110 mmHg and IFB ≥ 30 mmHg	0	1 (1.1)	1 (0.9)

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Parameter	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy NPM1-m R/R AML (N=112) n (%)
≥20 mmHg increase from baseline	6 (30.0)	13 (14.1)	19 (17.0)
Heart Rate			
ABSV <50 bpm and DFB ≥20 bpm	0	1 (1.1)	1 (0.9)
ABSV ≥120 bpm and IFB ≥30 bpm	1 (5.0)	4 (4.3)	5 (4.5)
Weight			
≥10% DFB	4 (20.0)	17 (18.5)	21 (18.8)

Source: KO-MEN-001 CSR, Table 14.3.5.4

The Applicant's Position:

There were no clinically relevant changes to vital signs with ziftomenib treatment.

Electrocardiograms (ECGs) / QT

Data:

In the 600 mg QD Monotherapy NPM1-m R/R AML population, TEAEs of electrocardiogram QT prolonged (12 patients [10.7%]), atrial fibrillation (3 patients [2.7%]), bundle branch block (1 patient [0.9%]), electrocardiogram T wave abnormal (1 patient [0.9%]), and ventricular tachycardia (1 patient [0.9%]) were reported. Of these, events of electrocardiogram QT prolonged in 3 patients (2.7%) and bundle branch block in 1 patient (0.9%) were assessed as related to ziftomenib. Review of the patients with ziftomenib-related events of electrocardiogram QT prolonged (Grade 2=1 patient, Grade 3=2 patients) identified that all 3 patients were on multiple concomitant QT prolonging medications; 2 patients 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 ECG-related SAEs. TEAEs of electrocardiogram QT prolonged in 4 patients (3.6%) and a ziftomenib-related TEAE of bundle branch block in 1 patient (0.9%) led to ziftomenib dose interruption. A ziftomenib-related TEAE of electrocardiogram QT prolonged in 1 patient (0.9%) led to ziftomenib dose reduction. There were no ECG-related TEAEs that led to ziftomenib discontinuation. Refer to Module 2.7.4, Section 4.1.1 (narrative portion of ISS).

Concentration-corrected QT interval (QTc), by time point, categorical and morphological analyses of ECGs from 31 patients in KO-MEN-001 Parts 1a and 1b were conducted to assess the cardiodynamic effects of ziftomenib (KO-PK-0003).

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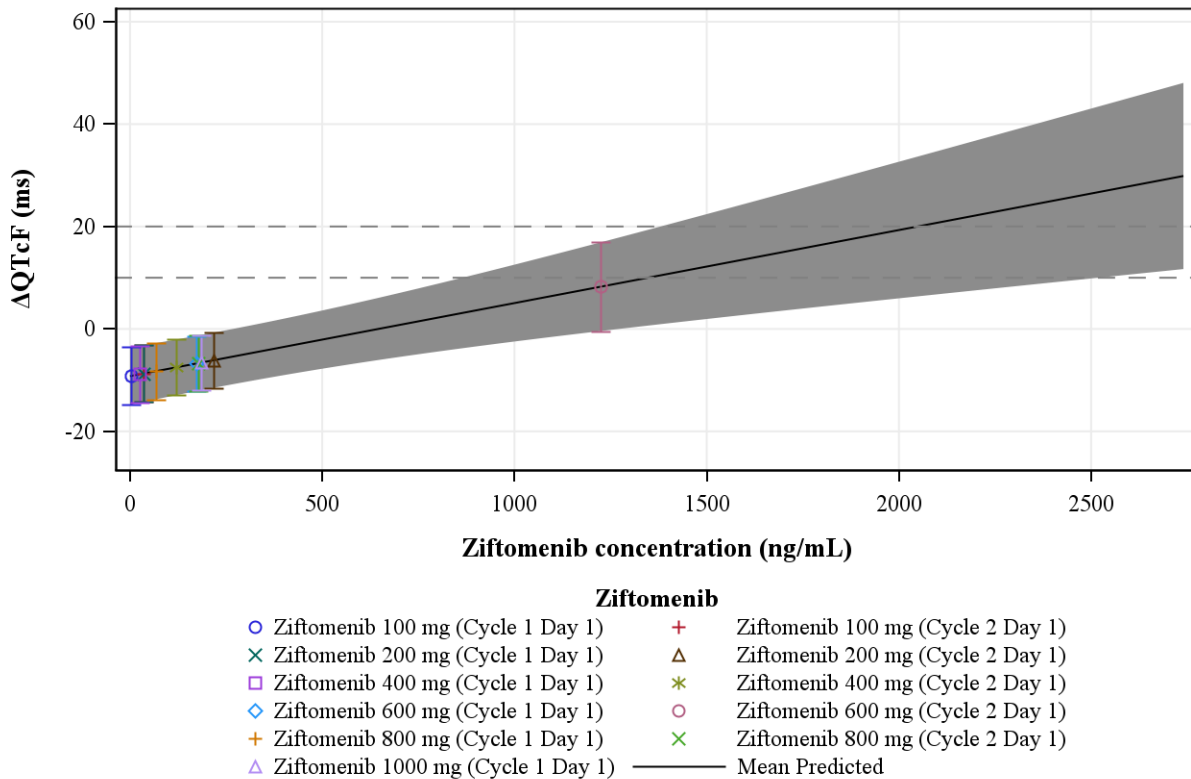
The relationship between baseline-corrected QTcF (Δ QTcF) and plasma concentrations of ziftomenib (and metabolites KO-516 and KO-739) were investigated using a linear mixed-effects modeling approach. The full model included Δ QTcF as the dependent variable, plasma concentration of ziftomenib as the explanatory variables, centered baseline QTcF (ie, baseline QTcF for individual patient minus the population mean baseline QTcF for all patients) as an additional covariate, a fixed intercept (ie, a population mean intercept), and random effects on intercept and slopes per patient. The model-predicted effect and its 2-sided 90% confidence interval (CI) for Δ QTcF (ie, the sum of slope estimate $\times$ concentration for all included analytes + population mean intercept) at these sets of concentrations were obtained. The predictions were based on maximum plasma concentration ($C_{\max}$) on Cycle 1 Day 1 and Cycle 2 Day 1. If the upper bound of the 2-sided 90% CI (equivalent to the upper bound of the 1-sided 95% CI) of the model-predicted QTc effect (Δ QTcF) was below 10 ms at clinically relevant plasma levels, it could be further concluded that ziftomenib did not cause clinically relevant QTc prolongation within their observed plasma concentration ranges. Based on this concentration-QTc analysis, an effect on Δ QTcF with 90% upper confidence interval (UCI) exceeding 10 ms can be predicted for ziftomenib plasma concentrations of approximately 865 ng/mL, and with 90% UCI exceeding 20 ms can be expected at approximately 1380 ng/mL (Applicant Figure 3). At steady state, ziftomenib mean $C_{\max}$ is 881 ng/mL at 600 mg QD, thus demonstrating that ziftomenib had no clinically significant effect on QTc by excluding an increase of >20 ms at the 600-mg dose level. Categorical analysis demonstrated that there were no QTcF prolongation of >480 ms or >500 ms or Δ QTcF >60 ms. Additionally, ziftomenib had no clinically significant effect on heart rate or on cardiac conduction (ie, the PR and QRS intervals).

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Applicant Figure 3: Applicant - Model-Predicted Δ QTcF Interval at Geometric Mean Peak Ziftomenib Plasma Concentrations (Model E)



Source: Module 2.7.4/ISS, Figure 1

The Applicant's Position:

Overall, ECG parameters showed no clinically meaningful changes over time and ziftomenib treatment had no clinically significant effect on QTc according to the concentration-QT assessment. Ziftomenib is not associated with clinically meaningful QTc prolongation.

Immunogenicity

The Applicant's Position:

Not applicable. No immunogenicity assessments were performed.

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8.3.5. Analysis of Submission-Specific Safety Issues

8.3.5.1. Differentiation Syndrome

The Applicant's Position:

Preclinical PK/pharmacodynamic studies revealed that ziftomenib induces terminal differentiation and apoptosis, mechanisms that can manifest as DS in clinical settings. As expected, ziftomenib-related DS was observed throughout all phases of Study KO-MEN-001.

Consistent with other targeted agents for the treatment of AML, differentiation syndrome emerged as a risk in Study KO-MEN-001 (Phase 1 Part 1a) in 1 patient with R/R *KMT2A-r* AML in the 1000 mg cohort experienced Grade 4 DS and subsequently died secondarily due to cardiac arrest. In Phase 1 Part 1b of Study KO-MEN-001, 17 patients (32.1%; predominantly *KMT2A-r*) experienced ziftomenib-related DS, including a Grade 5 (fatal) event in a patient with R/R *KMT2A-r* AML at the 200 mg dose level. Following the Grade 5 event, the DS mitigation guidance was issued, and enrollment of patients with R/R *KMT2A-r* AML was eventually closed.

A DS mitigation guidance was subsequently developed and included additional monitoring on Days 4 and 10 for evidence of rising white blood cell count with peripheral evidence of myeloid differentiation as well as coagulation and inflammatory markers. Monitoring for specific symptoms that may be possible signs of DS was detailed. Finally, sites were instructed to proceed with early ziftomenib interruption and institution of steroid therapy at the time of suspicion of a DS event. Following implementation of this DS guidance, no additional Grade 4 or 5 events were reported in either genotype.

A DS identification algorithm based on Montesinos 2009 and updated with Norsworthy 2020 was developed. A DS dataset encompassing all confirmed DS and potential DS cases (identified using the algorithm based on Norsworthy 2020) is included as 'adrsadj' in the KO-MEN-001 study folder and discussed in the KO-MEN-001 CSR.

Overall, in the 600 mg QD monotherapy *NPM1-m* R/R AML safety analysis population, 27 patients (24.1%) experienced a TEAE of DS, with a median time to the first event of DS being 15.0 days (range: 3 to 46 days). There were 16 patients (14.3%) who experienced an SAE of DS, of which all were considered related to ziftomenib treatment. Fifteen patients (13.4%) experienced an event of DS of a CTCAE Grade 3, all of which were considered related to ziftomenib treatment. The DS mitigation plan outlined in Study KO-MEN-001 included immediate treatment interruption for a suspected DS event; there were 15 (13.4%) patients who experienced a TEAE of DS that lead to a ziftomenib dose interruption. Although these DS events were considered serious, most cases were manageable per the DS mitigation guidance, with only 2 (1.8%) patients discontinuing ziftomenib treatment due to DS, 1 patient (0.9%) experiencing an event of DS that led to a dose reduction, and no patients having a CTCAE Grade 4 or 5 DS event. No patients in the 600 mg QD monotherapy *NPM1-m* R/R AML safety analysis population experienced TEAEs of DS that led to death.

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These events are consistent with other targeted AML agents. The Sponsor proposes language in the non-REMs medication guide and specific label language denoting the risks and procedures related to potential cases of DS arising during ziftomenib treatment.

8.3.5.2. Tumor Lysis Syndrome

The Applicant's Position:

Given the nonclinical activity and tumor regression pattern of ziftomenib in multiple tumor models in rodents, tumor lysis syndrome was a potential risk during the development of ziftomenib. Among patients in the 600 mg QD monotherapy *NPM1*-m R/R AML safety analysis population, 2 patients (1.8%) experienced a TEAE of TLS, with none of these events being considered related to ziftomenib treatment. Both events of TLS were of a CTCAE Grade 3, and 1 of the events was considered an SAE. None of the events lead to dose reduction, interruption, or discontinuation of ziftomenib treatment. The review of TLS events did not indicate a relationship between ziftomenib treatment and TLS development.

8.3.5.3. Drug-Induced Liver Injury

Data:

Based on findings in preclinical toxicology studies suggestive of adverse effects on the hepatobiliary system, drug-induced liver injury was a potential risk during the development of ziftomenib. Hy's law cases were defined as concurrent (within 7 days) AST or ALT $>3 \times$ upper limit of normal (ULN) and total bilirubin $>2 \times$ ULN (and ALP $<2 \times$ ULN or missing). In the 600 mg QD monotherapy *NPM1*-m R/R AML population, there were 2 patients (1.8%) who met potential Hy's law criteria (Applicant Table 23). Each patient had pre-existing, comorbid conditions prior to initiation of ziftomenib (bilirubin excretion disorder, blood ALP increased, blood bilirubin increased, and AST increased) and concomitant SAEs (cholecystitis and *Escherichia* sepsis), which, therefore, ruled out an event of Hy's law. Overall, observed hepatic changes were generally mild to moderate and well managed according to Study KO MEN 001 procedures.

Applicant Table 23: Applicant - Potential Hy's Law Cases

	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy <i>NPM1</i>-m R/R AML (N=112) n (%)
ALT			
>3×ULN	1 (5.0)	18 (19.6)	19 (17.0)

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	Part 1b EAS 600 mg QD (N=20) n (%)	Phase 2 mITT 600 mg QD (N=92) n (%)	600 mg QD Monotherapy NPM1-m R/R AML (N=112) n (%)
>5×ULN	0	8 (8.7)	8 (7.1)
>10×ULN	0	3 (3.3)	3 (2.7)
AST			
>3×ULN	1 (5.0)	14 (15.2)	15 (13.4)
>5×ULN	0	6 (6.5)	6 (5.4)
>10×ULN	0	3 (3.3)	3 (2.7)
Total Bilirubin >2×ULN	0	8 (8.7)	8 (7.1)
Concurrent (AST or ALT) >3×ULN and Total Bilirubin >2×ULN	0	3 (3.3)	3 (2.7)
Potential Hy's Law			
Concurrent (AST or ALT) >3×ULN and Total Bilirubin >2×ULN and (ALP <2×ULN or missing)	0	2 (2.2)	2 (1.8)

Source: KO-MEN 001 CSR, Table 14.3.4.1.4

The Applicant's Position:

The occurrence of potential Hy's law cases was rare with ziftomenib treatment and largely consistent with the complications of the heavily pre-treated underlying condition. Ziftomenib is not considered associated with DILI.

8.3.5.4. Bleeding Events

The Applicant's Position:

Bleeding events are frequently seen in patients with active AML due to underlying marrow dysfunction with associated thrombocytopenia. More common bleeding events, such as epistaxis, have been reported in 15.1% of patients receiving ivosidenib (DiNardo et al, 2018), 17.1% of patients receiving gilteritinib (Perl et al, 2019), and 26.6% of patients receiving revumenib monotherapy (Issa et al, 2023).

In the 600 mg QD monotherapy NPM1-m R/R AML population, there were no CTCAE Grade 4 or 5 bleeding events. There were 14 patients (12.5%) who reported a TEAE of epistaxis, with 2 (1.8%) patients reporting a CTCAE Grade 3 event and none being considered related to ziftomenib treatment. There were 4 patients (3.6%) who experienced a Grade 3 lower

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gastrointestinal hemorrhage, which was ziftomenib-related in 1 patient (0.9%), and 1 patient (0.9%) had a Grade 3 subdural hematoma, which was assessed as not related to ziftomenib.

Thrombotic events occur in about 8% to 9% of patients with newly diagnosed nonacute promyelocytic leukemia (APL; Libourel et al, 2016). Data on disseminated intravascular coagulation (DIC) in non-APL AML are fewer, but prevalence suggests 8.5% to 25% at presentation and further events with the commencement of chemotherapy (Ten Cate and Leader, 2021, Uchiumi et al, 2007). Overall, DIC was rare occurring in 4 patients (3.6%) in the 600 mg QD monotherapy *NPM1*-m R/R AML population, with the event in 1 patient (0.9%) being considered related to ziftomenib treatment. A Grade 3 event of pulmonary embolism was reported in 1 patient (0.9%) in the 600 mg QD monotherapy *NPM1*-m R/R AML safety analysis population and was assessed as not related to ziftomenib. Deep vein thrombosis was reported in 3 patients in the 600 mg QD monotherapy *NPM1*-m R/R AML population, and all were assessed as not related to ziftomenib.

Taken together, these data support that ziftomenib monotherapy does not increase bleeding and thrombotic events over what is observed in an AML population.

8.3.5.5. Febrile Neutropenia and Infection

The Applicant's Position:

Neutropenic fever occurs in up to 80% of patients receiving chemotherapy for hematological malignancies, including AML, with a risk of major complications of 25% to 30% and fatality rates of 11%, increasing up to 50% when accompanied with sepsis and/or septic shock (Taplitz et al, 2018). In the 600 mg QD monotherapy *NPM1*-m R/R AML population, febrile neutropenia was reported in 25 patients (22.3%) and 20 patients (17.9%) had events that were considered serious. Three patients (2.7%) experienced an event of febrile neutropenia that was considered related to ziftomenib treatment.

Due to neutropenia and being immunocompromised from both disease and treatment, infectious complications are common in AML patients. Pneumonia is one of the more common events occurring in AML patients, reported in 37% of AML patients receiving palliative therapy and 13.7% of patients receiving induction therapy (Tober et al, 2023). For patients receiving monotherapy with gilteritinib or ivosidenib, pneumonia was reported in 17.5% and 14.7% of patients, respectively, with Grade ≥ 3 pneumonia occurring in 11.8% and 11.6% of patients, respectively (Perl et al, 2019, DiNardo et al, 2018). In front-line combination therapy with venetoclax, 23% of patients developed pneumonia, including 20% with Grade ≥ 3 (DiNardo et al, 2018). In the 600 mg QD monotherapy *NPM1*-m R/R AML population, 24 patients (21.4%) reported an event of pneumonia, with 17 (15.2%) patients having of an event of a CTCAE Grade ≥ 3 and 12 patients (10.7%) reporting an SAE of pneumonia. None of the events of pneumonia were considered related to ziftomenib treatment. Additional details are provided in Section 2.1.9.3 of Module 2.7.4 (narrative portion of ISS).

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Overall, the results are consistent with a patient population receiving therapy for AML and there is no additive infection risk with ziftomenib treatment.

8.3.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Not applicable, there were no patient-reported clinical outcome assessments collected.

8.3.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

No subgroup analysis of the integrated safety data was performed. Population PK modeling was used to evaluate the impact of intrinsic factors on ziftomenib PK. Disease state was identified as a statistically significant covariate. However, as ziftomenib dose optimization was conducted in patients with R/R *NPM1*-m AML, no additional dose adjustment was necessary. Based on the population PK analysis, age, body weight, height, body mass index, body surface area, estimated glomerular filtration rate, serum creatinine, bilirubin, albumin, ALP, ALT, AST, sex, race, ethnicity, mutation type, renal impairment (mild or moderate), or hepatic impairment (mild or moderate) did not affect the PK of ziftomenib. Hence, no dose adjustment is required for any of the intrinsic factors.

8.3.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable; no safety specific studies were conducted.

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Not applicable; no human carcinogenicity or tumor development studies were conducted.

Human Reproduction and Pregnancy

Data:

There are no data available in pregnant women exposed to ziftomenib to assess the risks of ziftomenib treatment on pregnancy in humans and no pregnancies have been reported in ziftomenib clinical studies at the time of data cutoff.

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Based on findings from the embryo-fetal toxicity study in mice, ziftomenib is considered teratogenic and caused adverse developmental outcomes in mice at a level that was 3 times the proposed human dose exposure level of 600 mg QD. Administration of ziftomenib was not associated with maternal toxicity at any dose level (KO-TOX-0018). Ziftomenib was neither mutagenic nor clastogenic/aneugenic in standard in vitro and in vivo genotoxicity assays.

The Applicant's Position:

No pregnancies have been reported in the ziftomenib clinical studies to date. Ziftomenib may cause fetal harm when administered to a pregnant woman. Considering the 5 half-lives of ziftomenib, it is advised that female of reproductive potential and males with partners of reproductive potential use effective contraception during treatment and for 2 weeks after the last dose.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Not applicable; ziftomenib has not been investigated in pediatric subjects.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

There were no reports of overdose with ziftomenib treatment. No studies of drug abuse or dependence were conducted with ziftomenib. Ziftomenib is not chemically or pharmacologically similar to drugs with known abuse potential, and it does not produce known psychoactive effects. Studies on withdrawal and rebound with ziftomenib were not conducted in this patient population.

The Applicant's Position:

Neither the effects of ziftomenib nor an antidote to overdose are known. No information is available regarding withdrawal or rebound effects of ziftomenib.

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable; ziftomenib has not been approved or marketed for commercial use in any country.

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Expectations on Safety in the Postmarket Setting

The Applicant's Position:

The safety profile in the postmarketing setting is expected to be similar that observed in the clinical trial setting, anticipated to be acceptable and manageable with appropriate labeling, in the indicated population.

8.3.11. Integrated Assessment of Safety

Data:

The pivotal study, Study KO-MEN-001, was the primary source for the evaluation of the safety of ziftomenib 600 mg QD as monotherapy for the treatment of R/R AML in patients with *NPM1*-m (N=112). Sponsor data and positions for the Integrated Summary of Safety (ISS) is provided in the preceding sections of this document.

The Applicant's Position:

The overall safety profile of ziftomenib at the recommended dosage is acceptable for its intended use as palliative treatment of patients with R/R AML *NPM1* mutations. Risk management can adequately be managed through clear product labeling and monitoring for the important identified risk of DS and embryo-fetal risk (based only on nonclinical data). Labeling will include a warning for the serious risks, instructions for monitoring, and dose modification for toxicities. A non-REMS medication guide will inform and educate patients of the risk of DS and when to seek immediate medical attention. Ziftomenib had no clinically relevant effect on liver function and QTc or other ECG parameters. The safety, tolerability, and lack of myelosuppression of ziftomenib in this frail population support its role as a palliative therapy, reinforcing a favorable risk-benefit profile.

THE FDA'S POSITION

8.3.1. Safety Review Approach

Selection of the Safety Population

The safety database includes data from 359 treatments in 353 unique participants. These treatments were provided on three clinical trials (KO-MEN-001, KO-MEN-007, and KO-MEN-008), in addition to three substudies of the main KO-MEN-001 protocol. FDA Table 38 below shows the studies, the dosing of ziftomenib that was explored in each study, and the number of participants enrolled and treated at the time of the database cutoff. For the 6 participants who received multiple treatments:

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- Two participants were initially enrolled on KO-MEN-001 (ziftomenib monotherapy) and then were subsequently enrolled on KO-MEN-007 and received venetoclax + azacitidine + ziftomenib for R/R AML
- Three participants were initially enrolled on the newly diagnosed 7+3 plus ziftomenib cohort of KO-MEN-007 and were subsequently enrolled on the venetoclax + azacitidine + ziftomenib cohort of KO-MEN-007.
- One participant was initially enrolled on the newly diagnosed 7+3 plus ziftomenib cohort on KO-MEN-007 and subsequently enrolled on the FLAG-IDA ziftomenib cohort of KO-MEN-008 for R/R AML.

FDA Table 38. FDA Breakdown of Safety Database by Dose and Disease

Study Identifier	Disease	Dose	N
KO-MEN-001MAIN	AML	50 mg	1
KO-MEN-001MAIN	AML	100 mg	1
KO-MEN-001MAIN	AML	200 mg	23
KO-MEN-001MAIN	AML	400 mg	5
KO-MEN-001MAIN	AML	600 mg	133
KO-MEN-001MAIN	AML	800 mg	11
KO-MEN-001MAIN	AML	1000 mg	1
KO-MEN-001SS1	AML	600 mg	7
KO-MEN-001SS2	AML	600 mg	4
KO-MEN-001SS3	ALL	200 mg	4
KO-MEN-001SS3	ALL	400 mg	1
KO-MEN-007	AML	200 mg	36
KO-MEN-007	AML	400 mg	32
KO-MEN-007	AML	600 mg	78
KO-MEN-008	AML	100 mg	7
KO-MEN-008	AML	200 mg	15

Source: FDA analysis using adsl.xpt from SDN 0015 data cut March 21, 2025

The FDA pooled the population of patients slightly differently than presented in by the Applicant (FDA Table 39). The FDA considered the pooled population of patient with R/R AML with an *NPM1m* treated at the proposed monotherapy dose as the key safety population for labeling (N=112, N= 20 Phase 1b + N=92 Phase 2). The FDA then considered the whole population of R/R AML patients treated with ziftomenib monotherapy from KO-MEN-001 (N=175) as another key population to review. Lastly, the FDA considered the population of all ziftomenib treated patients in both monotherapy and combination therapy studies as the ISS population (N=353).

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FDA Table 39. Composition of safety analysis sets

	KO-MEN-001 MAIN (N=175)			KO-MEN-001 SS1	KO-MEN-001 SS2	KO-MEN-001 SS3	KO-MEN-007 (N=146)		KO-MEN-008 (N=22)		All
Genetic	KMT2A-r	NPM1-m	Other	Other	Other	KMT2A-r ^A	KMT2A-r	NPM1-m	KMT2A-r	NPM1-m	
Zifto Dose											
50 mg	1	0	0	0	0	0	0	0	0	0	1
100 mg	0	0	1	0	0	0	0	0	0	0	8
200 mg	14	6	3	0	0	4	21	15	10	5	78
400 mg	1	1	3	0	0	1	18	14	0	0	38
600 mg	18	112	3	7	4	0	28	50	0	0	222
800 mg	4	1	6	0	0	0	0	0	0	0	11
1000 mg	1	0	0	0	0	0	0	0	0	0	1
total	39	120	16	7	4	5	67	79	10	12	359

Source: FDA analysis using adsl.xpt from SDN 0015 data cut March 21, 2025

^A: patients with ALL.

Green highlight represents the main safety population. Blue highlight represents the monotherapy treated population of study KO-MEN-001. ISS is 359 treatments - 6 participants with two treatments N=353

8.3.2. Review of the Safety Database

Overall Exposure

For all treated participants (N = 359 exposures in 353 patients), the median duration of initial treatment was 63 days. For the pivotal safety population (N = 112), the median duration of initial treatment was 67.5 days (range 2-654 days). FDA Table 40 shows the maximum duration of treatment for patients in the FDA safety populations.

FDA Table 40. Duration of exposure in Treatment Period 1

Treatment Duration	NPM1m, 600 mg (N=112)	KO-MEN-001 (N=175)	ISS (N=359 exposures in 353 patients)
1-91 days	72 (64%)	232 (65%)	232 (65%)
92-182 days	22 (20%)	22 (13%)	87 (24%)
183-273 days	12 (11%)	12 (7%)	32 (9%)
> 273 days	6 (5%)	6 (3%)	8 (2%)

Source: FDA analysis using adsl.xpt and adexsum.xpt from SDN 0015 data cut March 21, 2025

Relevant Characteristics of the Safety Population:

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FDA Table 41 below show the demographic composition of the three FDA defined safety populations.

FDA Table 41. Demographic characteristic of FDA safety populations

	<i>NPM1m</i>	KO-MEN-001	ISS
	N = 112	N = 175	N = 353
Age			
Mean (SD)	65.6 (12.8)	61.5 (15.9)	59.3 (16)
Median (Range)	69 (22–86)	66 (18–86)	64 (18–90)
< 65 years; n (%)	42 (38)	81 (46)	182 (52)
≥ 65 years; n (%)	70 (63)	94 (54)	171 (48)
Sex; n (%)			
Female	63 (56)	93 (53)	185 (52)
Male	49 (44)	82 (47)	168 (48)
Race; n (%)			
White	88 (79)	135 (77)	246 (70)
Unknown	16 (14)	27 (15)	60 (17)
Asian	4 (3.6)	5 (2.9)	13 (3.7)
Black Or African American	2 (1.8)	4 (2.3)	19 (5)
Other	2 (1.8)	4 (2.3)	11 (3.1)
American Indian or Alaska Native	0	0	2 (0.6)
Multiple; n (%)	0	0	1 (0.3)
Ethnicity			
Not Hispanic Or Latino; n (%)	87 (78)	136 (78)	266 (75)
Not Reported/ Not Respond/ Unknown; n (%)	22 (20)	33 (19)	62 (18)
Hispanic Or Latino; n (%)	3 (2.7)	6 (3.4)	26 (7)

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Country			
United States; n (%)	52 (46)	102 (58)	276 (78)
Spain; n (%)	27 (24)	32 (18)	33 (9)
France; n (%)	15 (13)	23 (13)	26 (7)
Germany; n (%)	6 (5)	6 (3.4)	6 (1.7)
Canada; n (%)	5 (4.5)	5 (2.9)	5 (1.4)
Italy; n (%)	5 (4.5)	5 (2.9)	5 (1.4)
Belgium; n (%)	2 (1.8)	2 (1.1)	2 (0.6)
Geographic Region 1			
United States and Canada; n (%)	57 (51)	107 (61)	281 (80)
Europe and United Kingdom; n (%)	55 (49)	68 (39)	72 (20)
Baseline ECOG			
0; n (%)	30 (27)	44 (25)	85 (24)
1; n (%)	63 (56)	98 (56)	182 (52)
2; n (%)	19 (17)	33 (19)	64 (18)
3; n (%)	0	0	1 (0.3)
Not reported; n (%)	0	0	25 (7)
Disease			
AML; n (%)	112 (100)	175 (100)	349 (99)
ALL; n (%)	0 (0)	0 (0)	5 (1)
Source: FDA analysis using adsl.xpt			

Clinical Comment: The safety populations as delineated by the FDA show enrollment of a sufficient number of patients treated at the intended dose who had R/R AML with an NPM1 mutation. The ISS population including the remaining patients from Study KO-MEN-001 adds 241 ziftomenib-treated patients to the overall safety database. Comparison of demographics between these groupings shows a similar breakdown by age, sex, race, and ethnicity. The United States was the most common country for enrolled patients across both the population of participants with NPM1-m AML and the ISS. Finally, the exposure across these population were also similar (table exposure above).

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8.3.3. Adequacy of the Safety Database

The FDA agrees that the size of the safety database is adequate to identify common AEs. However, due to the number of patients treated for the proposed indication (monotherapy for R/R AML with *NPM1*-m) and the recommended dosage (600 mg daily) (n=112), rare events may be missed. Additionally, the duration of treatment is too short to establish the safety profile with long-term use as most patients were treated for less than 90 days. Therefore, additional data for long-term use may be required.

Adequacy of the Applicant's Clinical Safety Assessments

The FDA agrees with the Applicant's position. See the discussion concerning laboratory AEs versus laboratory value shift analysis in the FDA comments below.

Issues Regarding Data Integrity and Submission Quality

The quality of the safety data submitted was adequate to allow substantial primary review.

Categorization of Adverse Events

The FDA agreed with mapping of reported terms to preferred terms per MedDRA 27.0. Terms that referred directly to relapse, persistence of disease, or progression of AML were excluded from FDA's analyses. TEAEs were assessed by frequency (event per patient) and maximum grade reported.

The FDA reviewed the Applicant's grouped terms as above but also developed a list of grouped terms (GTs) based on preferred terms (PTs) that were reported in the ISS pool (see Appendix 14.5 for a table of FDA grouped terms used throughout FDA safety analyses unless otherwise noted). FDA assessed laboratory abnormalities as both reported AEs and by shifts from baseline labs. Since all patients in Study KO-MEN-001 presented with R/R acute leukemia, most patients had some level of abnormal baseline labs induced by the disease process. Therefore, analysis anchored from this abnormal baseline would not identify labs that normalized with control of the acute leukemia but later became abnormal again. Therefore, analysis of both lab shifts and lab abnormalities reported as TEAEs were evaluated to identify abnormal signals.

Routine Clinical Tests

The FDA agrees with the Applicant's position. See the discussion concerning laboratory AEs versus laboratory value shift analysis in the FDA comment above.

8.3.4. Safety Results

Deaths

The FDA performed an assessment of deaths, based on review of individual patient narratives, in patients enrolled on Study KO-MEN-001 that occurred within 30 days of the last dose of study drug. The FDA considered the Applicant's cause of death and either agreed with the cause of death and that it was not a fatal adverse reaction or flagged events as possible fatal adverse

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reactions and requested additional information on the cases with specific concerns noted below (FDA Table 42). This initial review identified 35 cases to obtain follow up information from the Applicant to complete adjudication of events.

FDA Table 42. FDA Initial Adjudication of Fatal Adverse Events

Need for additional information	FDA cause or concern	N
No further information required and not fatal adverse reaction	AML	31
	Infection	4
	Mitral valve disease	1
	multiorgan failure	2
	suicide	1
IR for further information and concern for fatal adverse reaction	agree with fatal adverse reaction	1
	agree with cause but consider it a fatal AR	16
	agree with DS fatal AR	1
	disagree with cause and consider DS as possible fatal AR	11
	disagree with cause and consider it fatal AR	5
	unclear, please provide additional details.	1
	total	74

The FDA categorized these requests into several categories of concerns: agree, agree with DS as fatal AR, agree with cause but consider the event a fatal AR, disagree with cause and consider DS as a possible fatal AR, disagree with cause and consider it a fatal AR, and unclear, please provide additional details. Given the context of the study, which enrolled patients with R/R AML without other available therapy, infectious events were ultimately attributable to persistent disease unless the patient had evidence of disease control (defined as < 5% bone marrow blasts). Based on this approach and the information, the Applicant was able to provide to the original narratives, we adjudicated these 35 events to 23 events of infection in the setting of persistent disease, 3 events of persistent disease, 1 event of stroke/persistent disease, 6 events of AR-DS, 1 event of AR-cardiac arrest, and 1 event of AR-infection (FDA Table 43). In the key safety population (n=112, NPM1-m AML treated at 600 mg QD), 4 fatal AEs occurred: 2 fatal ARs of DS, 1 fatal AR of infection, and 1 fatal AR of cardiac arrest. These were included in the USPI.

FDA Table 43. FDA Final Adjudication of Fatal Adverse Events

Patient ID	Study Day of Death	Applicant Cause of Death	Note for IR	Final FDA Adjudication
(b) (6)	73	AE : Febrile aplasia	Agree	AR-Infection

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(b) (6)

80	Coronary arrest	Consider cause a possible AR	AR-Cardiac arrest
22	AE: Fungal sinusitis	Consider cause a possible AR	infection/AML
18	Septic shock	Consider cause a possible AR	infection/AML
174	Sepsis	Consider cause a possible AR	infection/AML
42	Septic shock: Escherichia coli bacteremia, leukocytosis	Consider cause a possible AR	infection/AML
60	Unknown	Consider cause a possible AR	infection/AML
43	Stroke	Consider cause a possible AR	stroke/AML
20	Pneumonia	Consider cause a possible AR	infection/AML
18	Sepsis	Consider cause a possible AR	infection/AML
36	Sepsis	Consider cause a possible AR	infection/AML
75	Lung infection	Consider cause a possible AR	infection/AML
126	AE: Peritoneal infection	Consider cause a possible AR	infection/AML
74	Sepsis	Consider cause a possible AR	infection/AML
77	Septic shock	Consider cause a possible AR	infection/AML
56	AE: Pseudomonas bacteremia and deterioration of general condition	Consider cause a possible AR	infection/AML
36	Bowel perforation	Consider cause a possible AR	infection/AML
32	AE- Differentiation syndrome	Agree with DS	AR-DS
26	AE: Pneumonia	Disagree with cause; consider DS as possible cause	AML
16	Respiratory failure	Disagree with cause and consider DS as possible cause	AR-DS
2	Cardiac Arrest	Disagree with cause and consider DS as possible cause	AR-DS
19	Disseminated intravascular coagulation	Disagree with cause and consider DS as possible cause	AR-DS
10	AE: Sepsis	Disagree with cause and consider DS as possible cause	infection/AML
7	Encephalopathy	Disagree with cause and consider DS as possible cause	AR-DS
15	Disease progression	Disagree with cause and consider DS as possible cause	AR-DS

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(b) (6)			
22	Respiratory distress due to disease progression	Disagree with cause and consider DS as possible cause	AML
28	Lung infection	Disagree with cause and consider DS as possible cause	infection/AML
16	Respiratory compromise	Disagree with cause and consider DS as possible cause	infection/AML
26	AE: Lung infection	Disagree with cause and consider DS as possible cause	infection/AML
17	Cardiac arrest	Disagree with cause and consider it possible AR	infection/AML
30	Respiratory failure	Disagree with cause and consider it possible AR	infection/AML
204	Altered general condition	Disagree with cause and consider it possible AR	infection/AML
70	Respiratory failure	Disagree with cause and consider it possible AR	infection/AML
103	Disease progression	Disagree with cause and consider it possible AR	infection/AML
5	AML	Unclear, please provide additional details.	AML

Brief summaries of the cases of fatal adverse reactions are provided below.

Subject (b) (6) was a 75-year-old female with *NPM1*-m de novo AML who had previously received multiple treatments. She started ziftomenib at 600 mg on (b) (6). During treatment, she experienced pneumonia with fever and rash on day 49, leading to ziftomenib interruption on day 54. Although a bone marrow biopsy on day 64 showed morphologic leukemia-free state (0% blasts by aspirate, 4% by flow cytometry), allowing ziftomenib restart, the patient developed recurrent pneumonia and worsening dyspnea on day 71, ultimately leading to ziftomenib withdrawal. The patient died on day 73 (June 14, 2024) from febrile aplasia/infection. This infectious death was considered an AR since the patient was in a leukemia-free state at the time of occurrence.

Subject (b) (6) was a 76-year-old male with *NPM1*-m therapy-related AML that developed following treatment for diffuse large B-cell lymphoma. The patient had extensive cardiovascular comorbidities including coronary artery disease, atrial fibrillation, and hypertension, along with other conditions such as type 2 diabetes and obstructive sleep apnea. He was started on ziftomenib 600 mg daily in (b) (6), which successfully induced remission with 0% marrow blasts and count recovery by (b) (6). However, on (b) (6) approximately

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24-48 hours after developing symptoms of feeling cold and increased fatigue following a dental appointment, the patient was found deceased at home. Although the patient had cardiovascular comorbidities including coronary artery disease, atrial fibrillation, hypertension, and type 2 diabetes, his sudden death at home while in remission must be considered an AR.

Subject ^{(b) (6)} was a 33-year-old male with de novo *KMT2A-r* AML who had received multiple prior therapies including induction chemotherapy, salvage therapy, allogeneic stem cell transplant, and additional chemotherapy regimens before enrolling in a Phase 1/2 study of ziftomenib. The patient developed DS on Day 8 of ziftomenib treatment, which progressed to Grade 3 severity and required temporary drug interruption and treatment with dexamethasone and hydroxyurea. His clinical course was complicated by multiple bilateral pulmonary emboli on Day 19, followed by pneumonitis, and acute pericarditis with pericardial effusion on Day 22, accompanied by supraventricular tachycardia and lactic acidosis. Despite ongoing management including metoprolol for cardiac issues and continued dexamethasone tapering, the patient's condition deteriorated with persistent AML noted on Day 27 restaging, progressive pericardial effusion leading to cardiac tamponade, hypotension on Day 32, and ultimately cardiac arrest and death shortly after transfer to the intensive care unit.

CDTL Comment: While the review team acknowledges multiple confounding factors, the causal role of the documented AR of DS to the eventual patient death cannot be ruled out. As such, this is considered a fatal AR due to DS.

Subject ^{(b) (6)} was a 78-year-old male with *NPM1-m* AML who had an extensive medical history including cardiovascular conditions (atrial fibrillation, coronary artery disease, hypertension), chronic kidney disease, and various hematologic abnormalities. On Day 8 of ziftomenib treatment, the patient developed a Grade 3 device-related infection with *Streptococcus pyogenes* bacteremia in the setting of Grade 4 neutropenia, presenting with fever, fatigue, chills, and diaphoresis, which was treated with multiple antibiotics including vancomycin, cefepime, metronidazole, and later ceftriaxone. On Day 15, the patient developed Grade 2 DS with sudden oxygen requirement of 6L, dyspnea, and inspiratory wheezes, leading to ziftomenib interruption and treatment with dexamethasone and hydroxyurea. The patient's condition rapidly deteriorated on Day 16 with worsening hypoxemia requiring high-flow oxygen, rapidly climbing white blood cell counts, and ultimately Grade 5 respiratory failure that resulted in death on Day 16, with the patient declining escalation to intensive care.

CDTL Comment: Similarly, the prior S. pyogenes infection did not preclude DS from contributing to the death of this study participant. The rapid onset of respiratory failure in the context of hyperleukocytosis resulted in the attribution of this death as due to DS.

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Subject ^{(b) (6)} was a 42-year-old female with de novo *KMT2A*-r AML who had extensive prior treatment history including venetoclax, cytarabine, daunorubicin induction, and clofarabine with cytarabine and G-CSF, all resulting in progressive disease before enrolling in a Phase 1/2 study of ziftomenib. The patient had a complex medical history including proliferative disease, disseminated intravascular coagulation, and tumor lysis syndrome, and was hospitalized on Day -8 for AML treatment with cytarabine and hydroxyurea for elevated white blood cell count. On Day 1, she received her first and only dose of ziftomenib 1000 mg, but on Day 2 developed Grade 4 differentiation syndrome with rapidly rising WBC and elevated troponins, followed by Grade 5 cardiac arrest. Despite 11 minutes of cardiopulmonary resuscitation that restored pulse and transfer to intensive care with mechanical ventilation and pressors, the patient developed severe acidosis, coagulopathy consistent with DIC, and signs of anoxic brain injury, leading to withdrawal of care and death on Day 2 due to cardiac arrest secondary to DS.

Subject ^{(b) (6)} was a 58-year-old female patient with *KMT2A*-r AML. The patient had rapidly proliferative disease requiring hydroxyurea during screening and was treated with prednisone 40 mg daily (equivalent to 6 mg dexamethasone) from cycle 1 day 1 of ziftomenib therapy. On day 9, the patient was diagnosed with DS based on dyspnea, hypoxia, tachycardia, and increased white blood cell count, leading to treatment with hydroxyurea and dexamethasone 10 mg twice daily with initial clinical improvement. However, despite continued dexamethasone therapy, the patient subsequently developed severe bone pain, rising uric acid, and DIC, prompting ziftomenib interruption and escalation to higher dexamethasone doses (40 mg once, then 30 mg daily). The patient's condition continued to deteriorate with worsening DIC and tumor lysis syndrome (TLS) that was unresponsive to increased steroids, leading the investigator to conclude this represented worsening AML rather than DS, ultimately requiring treatment with increased hydroxyurea and IV cytarabine for progressive leukemia. However, contribution cannot be ruled out, particularly given rapid WBC rise after dexamethasone dose reduction. Therefore, conservative approach recommended that this case count as a DS-related death given uncertainty and multiple organ involvement.

Subject ^{(b) (6)} was a 63-year-old female with R/R *KMT2A*-r AML who had significant disease burden including extramedullary disease. One week prior to starting ziftomenib 200 mg daily, she was hospitalized for generalized weakness and failure to thrive due to aggressive AML, with baseline laboratory abnormalities including elevated creatinine (1.10 mg/dL from 0.87 mg/dL) and uric acid (8.3 mg/dL from 6.1 mg/dL) by cycle 1 day 1, along with screening ECGs showing premature atrial and ventricular complexes. After receiving four doses of ziftomenib while on prednisone 40 mg daily, the patient developed encephalopathy (deemed multifactorial including opiate use), hypoxia requiring oxygen supplementation, atrial fibrillation with rapid ventricular rate, and leukocytosis with high circulating blasts but notably without evidence of differentiation (no monocytosis, with only 13% lymphocytes and 1% monocytes). The investigator assessed these findings as consistent with rapidly worsening AML rather than DS, given the absence of

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peripheral differentiation, pre-existing renal insufficiency, hypoxia attributed to cardiac arrhythmias in the setting of prior cardiac abnormalities, and the patient's overall clinical deterioration preceding ziftomenib initiation. However, FDA considered this DS as patient underwent rapid decompensation with WBC rising rapidly with multiple organ involvement in only a few days after starting ziftomenib treatment with 3 out of 4 Montesinos criteria (moderate to severe, likely severe given oxygen saturation of 84% likely indicated dyspnea as well) at the time of death.

Subject (b) (6) was a 76-year-old male with AML arising from antecedent hematological disease, specifically chronic myeloid leukemia, who had received multiple prior therapies including cytarabine and idarubicin induction, cytarabine consolidation and salvage, and azacitidine salvage before enrolling in a Phase 1/2 study of ziftomenib. The patient received ziftomenib 600 mg starting on Day 1 but developed Grade 2 systemic inflammatory response syndrome on Day 7, followed by Grade 3 constipation requiring hospitalization on Day 8 that led to ziftomenib interruption and eventual discontinuation on Day 9 (last dose Day 7). His clinical course was complicated by Grade 3 TLS on Day 9 treated with rasburicase, Grade 3 acute kidney injury on Day 10 with peripheral edema (initially suspected to be differentiation syndrome and treated with dexamethasone and furosemide), and progressive deterioration with persistent hypercalcemia, hyperphosphatemia, measurable uric acid, confusion, altered mental status, and oxygen dependence by Day 14. The patient died on Day 15 with ongoing systemic inflammatory response syndrome, tumor lysis syndrome, peripheral edema, and acute kidney injury at the time of death. Patient with multiorgan involvement including acute respiratory distress, acute renal failure, peripheral edema, and biological inflammatory syndrome. after starting ziftomenib treatment. Therefore, conservative approach recommended that this fatal event count as DS-related death given uncertainty and multiple organ involvement.

Serious Adverse Events

The FDA performed an analysis of all-grade treatment-emergent SAEs occurring in $\geq 2\%$ of subjects in the main safety population of Study KO-MEN-001, which is presented in FDA Table 44 below. The results agreed with the Applicant's analysis overall but differed in the rates of grouped events. Most of the SAEs are expected during the care of patients with R/R AML such as infections and bleeding events. DS and leukocytosis are the two SAEs whose rates are likely due to ziftomenib treatment and its mechanism of action as an agent that releases the genetic block to blast differentiation.

FDA Table 44. FDA analysis of TESAE's occurring >2% of subject in key safety population of Study KO-MEN-001

	Ziftomenib: 600 mg
	N = 112
	n (%)

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Version date: March 1, 2024 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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	All	Grade
	Grade	3-4
Any SAE	89 (79)	59 (53)
Infections and infestations		
Infection (GT)	33 (29)	22 (20)
Bacterial infection (GT)	18 (16)	14 (13)
Viral infection (GT)	5 (4.5)	5 (4.5)
Fungal infection (GT)	3 (2.7)	1 (0.9)
Blood and lymphatic system disorders		
Febrile neutropenia	20 (18)	20 (18)
Leukocytosis (GT)	5 (4.5)	3 (2.7)
Anaemia	3 (2.7)	3 (2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Differentiation syndrome	16 (14)	14 (13)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea (GT)	7 (6)	3 (2.7)
Respiratory failure	4 (3.6)	1 (0.9)
Gastrointestinal disorders		
Diarrhoea (GT)	5 (4.5)	3 (2.7)
General disorders and administration site conditions		
Pyrexia	5 (4.5)	3 (2.7)
Vascular disorders		
Haemorrhage (GT)	4 (3.6)	2 (1.8)
Source: FDA analysis using adsl.xpt and adae.xpt		
GT: indicated FDA grouped term		

The FDA conducted the same analysis for TESAEs in the ISS population as shown in FDA Table 45 below. Again, most TESAEs were consistent with event that occur in patients with R/R AML and similar to the rates observed in the main safety population from Study KO-MEN-001.

FDA Table 45. FDA analysis of TESAЕ’s occurring >2% of subject in ISS population

SAE	Overall Grade 1-5 N = 353	Overall Grade 3-4 N = 353
Any SAE	267 (76)	193 (55)
Infections and infestations		
Infection (GT)	103 (29)	76 (22)

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Bacterial infection (GT)	39 (11)	33 (9)
Viral infection (GT)	12 (3.4)	11 (3.1)
Fungal infection (GT)	10 (2.8)	6 (1.7)
Blood and lymphatic system disorders		
Febrile neutropenia	74 (21)	74 (21)
Leukocytosis (GT)	11 (3.1)	6 (1.7)
Diarrhoea (GT)	15 (4.2)	12 (3.4)
Nausea (GT)	8 (2.3)	7 (2)
General disorders and administration site conditions		
Pyrexia	12 (3.4)	4 (1.1)
Fatigue (GT)	8 (2.3)	8 (2.3)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain (GT)	7 (2)	5 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Differentiation syndrome	36 (10)	29 (8)
Respiratory, thoracic and mediastinal disorders		
Respiratory failure	7 (2)	3 (0.8)
Dyspnoea (GT)	10 (2.8)	5 (1.4)
Vascular disorders		
Haemorrhage (GT)	20 (6)	13 (3.7)
Thrombosis (GT)	7 (2)	4 (1.1)
Source: FDA analysis using adsl.xpt and adae.xpt GT: indicated FDA grouped term		

Overall, the spectrum of TESAEs with ziftomenib were generally consistent with expected events in patients with R/R AML and those from therapy that induce differentiation.

Dropouts and/or Discontinuations

FDA conducted an analysis of TEAEs leading to dose interruptions in the main safety population of Study KO-MEN-001 as shown in FDA Table 46 below. This shows the results for TEAEs with a frequency of 2% or greater. TEAEs leading to dose interruptions occurred in 54% of patients in the main safety population of Study KO-MEN-001. The most frequent TEAEs leading to dose interruptions were infection, DS, febrile neutropenia, leukocytosis, pyrexia, electrocardiogram QT prolonged, and bacterial infection.

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FDA Table 46. FDA analysis of TEAE's leading to ziftomenib dose interruption in key safety population of Study KO-MEN-001 with a frequency of $\geq 2\%$

	600 mg	
	N = 112	
	n (%)	
	All-Grade	Grade 3-4
Any TEAE	61 (54)	50 (45)
Infection (GT)	17 (15)	17 (15)
Differentiation syndrome	15 (13)	11 (10)
Febrile neutropenia	6 (5)	6 (5)
Leukocytosis (GT)	5 (4.5)	3 (2.7)
Pyrexia	5 (4.5)	2 (1.8)
Electrocardiogram QT prolonged	4 (3.6)	4 (3.6)
Bacterial infection (GT)	3 (2.7)	3 (2.7)

Source: FDA analysis using adsl.xpt and adae.xpt
GT: indicated FDA grouped term

Clinical TL Note: There were several TEAEs leading to dose interruption that occurred in 2/112 participants (1.8%), which are not included in the table above but were rounded to 2% for inclusion in the USPI, including cardiac failure, cholecystitis, diarrhea, pruritus, and thrombosis.

The FDA conducted an analysis of TEAEs leading to dose reductions in the main safety population of Study KO-MEN-001 and found that 3.6% of patients had a TEAE leading to dose reduction with no one TEAE occurring in more than one patient.

The FDA conducted an analysis of TEAEs leading to dose discontinuations in the main safety population of Study KO-MEN-001 as shown in FDA Table 47 below. This shows the results for TEAEs with a frequency of 2% or greater. TEAEs leading to dose discontinuation occurred in 21% of patients in the main safety population of Study KO-MEN-001. The most frequent TEAE leading to dose discontinuation were infection and bacterial infection.

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FDA Table 47. FDA analysis of TEAE's leading to ziftomenib discontinuation in key safety population of Study KO-MEN-001 with a frequency of $\geq 2\%$

	600 mg	
	N = 112	
	All-Grade; n (%)	Grade 3-4; n (%)
Any TEAE	24 (21)	15 (13)
Infection (GT)	9 (8)	6 (5)
Bacterial infection (GT)	4 (3.6)	2 (1.8)

Source: FDA analysis using adsl.xpt and adae.xpt
GT: indicated FDA grouped term

Clinical TL Note: There were also cases of cardiac arrest (N=2) and differentiation syndrome (N=2) that resulted in discontinuation of ziftomenib, which occurred at rates of 1.8%. These were rounded to 2% for inclusion in Section 6.1 of the USPI.

Significant Adverse Events

The FDA agrees with the Applicant's assessment that blood cytopenias, infection, and DS were the most common severe TEAEs. The FDA conducted an analysis of all-grade and grade 3-4 TEAEs with FDA grouped terms in FDA Table 48 below, with infection further clarified as: bacterial, fungal, or viral infection, or infection without an identified pathogen. The FDA also notes that in the context of a single-arm study of patients with R/R AML, severe cytopenias are expected as the underlying disease progresses or fails to respond to treatment. With that context in mind, the rates of cytopenias observed on the study were not considered to occur at a rate higher than expected for the enrolled population.

Treatment Emergent Adverse Events

FDA tabulations of TEAEs agreed with the Applicant's with regard to the rate of any TEAE, grade 3 or 4 TEAEs, grade 5 TEAEs, and TEAEs leading to either dose discontinuations, dose reductions, or dose interruptions. FDA Table 48 shows the FDA tabulation of the most common grade all grade and grade 3- 4 TEAEs that occurred in at least 10% of subjects or were grade 3-4 in at least 5% of subjects on Study KO-MEN-001.

Due to the high rate of TEAEs observed in patients with R/R AML, the FDA identified those TEAEs that occurred in at least 20% of subjects or were grade 3-4 in at least 5% of subjects as those clinically relevant for ziftomenib labeling. These are marked in FDA Table 48 below with (*) following the preferred term and were included in labeling. Most laboratory TEAEs were not included in the USPI as they were better handled with the lab shift analysis discussed below. As the Applicant's analysis similarly showed, the most common TEAEs were GI toxicity, infectious complications, and cytopenias. As discussed above, infectious complications and cytopenias are expected from in patients with R/R AML. DS was another common TEAE that is not expected in

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the context of R/R AML unless patients are treated with differentiation inducing therapy. This is further discussed below. QTc prolonged occurred in 12% overall and 8% were grade 3 events. This is further discussed below and in Section 6.

FDA Table 48. FDA analysis of common TEAE's (Any grade $\geq$ 10% or grade 3-4 $\geq$ 5%) in key safety population of Study KO-MEN-001

	N = 112	
	All- Grade; n (%)	Grade 3-4; n (%)
Any TEAE	112 (100)	78 (70)
Gastrointestinal disorders		
Diarrhoea (GT)*	40 (36)	6 (5)
Nausea (GT)*	39 (35)	2 (1.8)
Constipation	20 (18)	2 (1.8)
Abdominal pain (GT)	16 (14)	1 (0.9)
Infections and infestations		
Infection (GT)*	58 (52)	31 (28)
Bacterial infection (GT)*	31 (28)	17 (15)
Viral infection (GT)*	18 (16)	6 (5)
Fungal infection (GT)	11 (10)	2 (1.8)
Urinary tract infection	11 (10)	2 (1.8)
Investigations		
Transaminases increased (GT)*	23 (21)	9 (8)
Platelet count decreased	15 (13)	15 (13)
Electrocardiogram QT prolonged	13 (12)	9 (8)
Weight decreased	13 (12)	0
White blood cell count decreased	8 (7)	7 (6)
Blood and lymphatic system disorders		
Febrile neutropenia*	25 (22)	25 (22)
Anaemia	25 (22)	23 (21)
Thrombocytopenia	22 (20)	22 (20)
Leukocytosis (GT)*	18 (16)	6 (5)
Neutropenia	15 (13)	15 (13)
General disorders and administration site conditions		
Fatigue (GT)*	38 (34)	9 (8)
Oedema (GT)*	33 (29)	3 (2.7)
Pyrexia	19 (17)	4 (3.6)
Metabolism and nutrition disorders		

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Hypokalaemia	29 (26)	13 (12)
Decreased appetite	19 (17)	1 (0.9)
Hyperglycaemia	14 (13)	10 (9)
Hypocalcaemia	11 (10)	4 (3.6)
Hypomagnesaemia	11 (10)	0
Respiratory, thoracic and mediastinal disorders		
Dyspnoea (GT)	20 (18)	4 (3.6)
Cough (GT)	11 (10)	0
Hypoxia*	10 (9)	6 (5)
Skin and subcutaneous tissue disorders		
Pruritus*	26 (23)	0
Rash (GT)	16 (14)	2 (1.8)
Nervous system disorders		
Taste disorder (GT)	13 (12)	0
Vascular disorders		
Haemorrhage (GT)*	42 (38)	9 (8)
Hypotension (GT)	18 (16)	4 (3.6)
Hypertension (GT)*	12 (11)	6 (5)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain (GT)*	31 (28)	4 (3.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Differentiation syndrome*	27 (24)	15 (13)
Injury, poisoning and procedural complications		
Fall	11 (10)	2 (1.8)
Renal and urinary disorders		
Renal impairment (GT)*	21 (19)	7 (6)
Source: FDA analysis using adsl.xpt and adae.xpt GT: indicated FDA grouped term *Indicates that term was included in USPI. Terms were included in the USPI if any grade $\geq$ 20% or grade 3-4 $\geq$ 5%.		

Laboratory Findings

The FDA analysis of laboratory shift tables was generally in agreement with the Applicant's results. However, it is important to note that the unique situation of R/R AML means that most patients present with baseline laboratory abnormalities which may persist. High baseline laboratory abnormalities obscure on-treatment worsening that might occur after resolution with remission attainment and hides prolonged abnormalities. Therefore, the FDA used a combination of laboratory shift analyses and laboratory values reported as TEAEs to capture laboratory AEs of clinical interest induced by ziftomenib treatment. To ascertain which labs were worsening

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with ziftomenib treatment above the background and were of clinical interest, a threshold of $\geq 10\%$ (*) and clinically meaningful were used to obtain the results in FDA Table 49 below.

Most laboratory shifts from baseline were mild, except for potassium decreased which showed a grade 3-4 shift in 22% of ziftomenib treated patients. However, it has been noted for decades that uncontrolled acute leukemia is associated with hypokalemia and total body potassium depletion.¹³ Therefore, it is hard to ascertain if the shifts seen on Study KO-MEN-001 are due to uncontrolled AML or ziftomenib treatment. Since electrolyte abnormalities have secondary consequences, they were included in ziftomenib labeling. Additionally, since uncontrolled or worsening acute leukemia is associated with elevations of lactate dehydrogenase and urate, worsening cytopenias, and coagulopathy, these labs shifts are shown in FDA Table 49 but were not included in the ziftomenib label.

FDA Table 49. FDA analysis of laboratory shifts from baseline grade to any grade higher than baseline or from baseline to max grade 3 or 4 in key safety population of Study KO-MEN-001

	N = 112	
	All-Grade n/N evaluable (%)	Grade 3-4 n/N evaluable (%)
Chemistry		
Potassium (mmol/L) – Decreased*	57/110 (52)	24/110 (22)
Aspartate Aminotransferase (U/L) – Increased*	57/109 (52)	4/109 (4)
Alanine Aminotransferase (U/L) – Increased*	53/109 (49)	7/109 (6)
Albumin (g/L) – Decreased*	56/109 (51)	5/109 (5)
Sodium (mmol/L) – Decreased*	54/110 (49)	3/110 (3)
Creatinine (umol/L) – Increased*	48/110 (44)	4/110 (4)
Alkaline Phosphatase (U/L) – Increased*	44/108 (41)	5/108 (5)
Bilirubin (umol/L) – Increased*	29/109 (27)	6/109 (6)
Potassium (mmol/L) – Increased*	28/110 (25)	6/110 (5)
Lactate Dehydrogenase (U/L) – Increased	24/110 (22)	0/110 (0)
Urate (umol/L) – Increased	18/108 (17)	0/108 (0)
Coagulation		
Prothrombin Intl. Normalized Ratio – Increased	40/108 (37)	1/108 (0.9)
Fibrinogen (g/L) – Decreased	20/91 (22)	16/91 (18)
Activated Partial Thromboplastin Time (s) – Increased	20/109 (18)	4/109 (3.7)

¹³ Lantz B, Carlmark B, Reizenstein P (1979). Electrolytes and whole body potassium in acute leukemia. Acta Medica Scandinavica; 206:45-50.

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Hematology		
Hemoglobin (g/L) – Decreased	72/110 (65)	62/110 (56)
Platelets (10 ⁹ /L) – Decreased	69/110 (63)	65/110 (59)
Lymphocytes (10 ⁹ /L) – Decreased	65/108 (60)	45/108 (42)
Leukocytes (10 ⁹ /L) – Decreased	65/110 (59)	56/110 (51)
Neutrophils (10 ⁹ /L) – Decreased	53/109 (49)	53/109 (49)
Lymphocytes (10 ⁹ /L) – Increased	21/108 (19)	2/108 (1.9)

Source: FDA analysis using adsl.xpt and adlb.xpt
*Indicates that only these select labs were included in USPI.
Note that certain laboratory values listed in the USPI were within 1% higher than FDA’s calculations; therefore, the FDA accepted the Applicant’s values for use in the USPI.

Vital Signs

The FDA agrees with the Applicant’s assessment of vital signs.

QT/Electrocardiograms (ECGs)

The FDA does not agree with the Applicant’s assessment that ziftomenib is not associated with clinically meaningful QTc prolongation. Please see the discussion of FDA modeling of ziftomenib concentration and QTc prolongation in Section 6. As shown in FDA Table 48, QTc prolonged was noted to occur at any grade in 12% of the key safety population with grade 3 events in 8% of the population.

Clinical Reviewer’s Comment: It is important to note that grade 3 QTc prolongation requires either an average QTc ≥ 501 ms or a > 60 ms increase from baseline. Moreover, for a QTc prolongation event to rise to grade 4, an associated clinical event of Torsade de pointes, polymorphic ventricular tachycardia, or other signs/symptoms of serious arrhythmia is required. While the treatment of patients in this single-arm study makes it difficult to attribute all QTc prolongation events to ziftomenib alone, since most patients were receiving concomitant medications (azole antifungals, antiemetics, antibiotics) commonly used in this population, the FDA decided that the combination of the concentration-dependent increase in QTc noted above, combined with the potential for inadvertent ziftomenib concentration increases from drug-drug interactions or food effects and standard use of supportive medications with QTc-prolonging potential, required the addition of a QTc prolongation warning and precaution to the label to mitigate this risk in clinical use.

Immunogenicity

The FDA agrees with Applicant’s position. The risk of immunogenicity for small molecules is low, and there was no indication in the TEAE analysis of an issue with immunologic problems.

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8.3.5. Analysis of Submission-Specific Safety Issues

Differentiation Syndrome

The FDA screened for potential DS cases by algorithm¹⁴ in Study KO-MEN-001, including review of the investigator-reported DS cases, and reviewed the narratives and other clinical data as provided by the Applicant in initially supplied narratives. The algorithm flagged 98 events in 80 study participants for review. These events were categorized as unlikely DS, possible DS, or DS; cases of possible DS were flagged for the Applicant to submit further explanation or a narrative if one was not previously required. Based on this adjudication process, FDA identified 57 cases of DS in 43 study participants, including 29 subjects within the key safety population of *NPM1*-m AML treated at 600 mg QD. It is important to note that DS was an important safety issue identified early in the ziftomenib development program which led to a clear focus on identifying cases of DS as they occurred in patients so that they were appropriately managed. This focus included continuous use of algorithmic screening of the safety database. The FDA review only identified 3 additional cases of DS that had not been previously noted. Two new cases of DS were noted above in the review of fatal ARs (subject (b) (6) and subject (b) (6) along with the up-grading of fatal ARs for 3 subjects (subject (b) (6), subject (b) (6) and subject (b) (6) that had previously been considered lower grade events of DS.

FDA Table 50 below shows a summary tabulation of the FDA-adjudicated events by genetic marker. There is a differential rate of DS observed when comparing participants with *KMT2A*-r and *NPM1*-m AML. This was observed early in the KO-MEN-001 study. The overall rate of DS was 29/120 (24%) in all patients with *NPM1*-m AML and 29/112 (26%) in the key safety population. This is in comparison to the DS rates that were observed early in the KO-MEN-001 study of patients with *KMT2A*-r AML that showed overall DS rates of 15/36 (42%). Moreover, the severity of DS was worse in the population of patients with *KMT2A*-r AML, who had 11/36 (31%) versus those with *NPM1*-m AML with 17/120 (14%) grade 3-5 events. Notably, grade 5 events were more common in the *KMT2A*-r population (4/36 (11%)) versus in the *NPM1*-m population overall (2/120 (2%)) or in the key *NPM1*-m safety population (2/112 (2%)).

FDA Table 50. FDA Adjudicated DS by grade and genetic subtype on Study KO-MEN-001

Maximum Grade	Genetic Subtype		
	<i>KMT2A</i> -r (n=36)	<i>NPM1</i> -m (n=120)	Other (n=16)
Grade 1	1 (3%)	3 (3%)	0
Grade 2	3 (8%)	9 (8%)	0
Grade 3	7 (19%)	15 (13%)	0

¹⁴ Norsworthy KJ, et al (2020). Differentiation syndrome with ivosidenib and enasidenib treatment in patients with relapsed or refractory IDH-mutated AML: A U.S. Food and Drug Administration Systematic Analysis. Clin Cancer Res; 26:4280-88.

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Grade 4	0	0	0
Grade 5	4 (11%)	2 (2%)	0
Total	15 (42%)	29 (24%)	0

Source: FDA analysis of adae.xpt, advs.xpt, adlb.xpt, adsl.xpt, and case narratives.

The rates of DS by genetic subtype and dose level are shown in FDA Table 51. Although all DS events in subjects with *NPM1*-m AML occurred at the 600 mg QD dose, events occurred in the participants with *KMT2A*-r AML at doses both higher and lower than the labeled dose for the proposed indication, including fatal events that occurred in patients with *KMT2A*-r at doses lower than the recommended dose. That fatal adverse reactions occurred in patients with *KMT2A*-r at a higher rate (4/39) than the occurred for the labeled indication (2/112) was included in the warning and precaution for differentiation syndrome in USPI. As noted by the Applicant, the higher rate and grade of DS observed in patients with *KMT2A*-r treated with ziftomenib along with the lower response rate observed led them to abandon ziftomenib monotherapy studies for these patients in favor of exploring combination therapies. It remains unclear why this differential effect was observed for ziftomenib and if any other menin inhibitor currently in development will show similar results.

FDA Table 51. FDA Adjudicated All-Grade DS by dose and genetic subtype on Study KO-MEN-001

Ziftomenib Dose	Genetic Subtypes		
	<i>KMT2A</i> -r (n=36)	<i>NPM1</i> -m (n=120)	Other (n=16)
50 mg	0/1 (0%)	0/0 (0%)	0/0 (0%)
100 mg	0/0 (0%)	0/0 (0%)	0/1 (0%)
200 mg	7/14 (50%)	0/6 (0%)	0/3 (0%)
400 mg	0/1 (0%)	0/1 (0%)	0/3 (0%)
600 mg	7/18 (39%)	29/112 (26%)	0/3 (0%)
800 mg	0/4 (0%)	0/1 (0%)	0/6 (0%)
1000 mg	1/1 (100%)	0/0 (0%)	0/0 (0%)

Source: FDA analysis of adae.xpt, advs.xpt, adlb.xpt, adsl.xpt, and case narratives.

8.3.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No clinical outcomes assessments were submitted.

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8.3.7. Safety Analyses by Demographic Subgroups

Drug-Demographic Interactions

TEAEs by Sex

FDA Table 52 shows TEAEs from the main safety population separated by sex and with at least 10% difference between males and females. It is interesting to note that, while the overall occurrence of TEAEs is 100% in either males or females, the occurrence of grade 3 and 4 events occurred more frequently in females (76% in females versus 61% in males). Moreover, almost all the risk differences that were observed were for more frequent occurrences in female patients, with the notable exception of DS, which was more frequent in males (31% of males versus 19% of females). As discussed above, most of the TEAEs that were observed on Study KO-MEN-001 are events that frequently occur in patients with R/R AML. Therefore, it is not clear that the events that occurred more often in females were due to ziftomenib treatment or how complications of the underlying AML vary by sex.

FDA Table 52. FDA analysis of TEAE's by sex with a risk difference $\geq 10\%$ between males and females in key safety population of Study KO-MEN-001

TEAEs	Male Grade 1-5 N = 49	Male Grade 3-4 N = 49	Female Grade 1-5 N = 63	Female Grade 3-4 N = 63	Risk Difference (Grade 1-5)
Any TEAE	49 (100)	30 (61)	63 (100)	48 (76)	0.00
Infection (GT)	20 (41)	10 (20)	38 (60)	21 (33)	-19.00
Fatigue (GT)	8 (16)	3 (6)	30 (48)	6 (10)	-32.00
Nausea (GT)	11 (22)	1 (2)	28 (44)	1 (1.6)	-22.00
Bacterial infection (GT)	7 (14)	3 (6)	24 (38)	14 (22)	-24.00
Musculoskeletal pain (GT)	9 (18)	1 (2)	22 (35)	3 (4.8)	-17.00
Differentiation syndrome	15 (31)	8 (16)	12 (19)	7 (11)	12.00
Pruritus	8 (16)	0	18 (29)	0	-13.00
Pyrexia	3 (6)	1 (2)	16 (25)	3 (4.8)	-19.00
Thrombocytopenia	7 (14)	7 (14)	15 (24)	15 (24)	-10.00
Dyspnoea (GT)	5 (10)	1 (2)	15 (24)	3 (4.8)	-14.00
Rash (GT)	3 (6)	0	13 (21)	2 (3.2)	-15.00

Source: FDA analysis of *adae.xpt* and *adsl.xpt*

TEAEs by Age

FDA Table 53 shows TEAEs from the main safety population separated by age groups of < 65 or ≥ 65 that had a risk difference greater than 10 between groups. Unexpectedly, grade 3-4 events were slightly more common in the younger age group (76% for <65 years old versus 66% for ≥ 65 years old). The remaining breakdown of TEAEs showed that most of the events were more

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common in the younger patients with only the hemorrhage and edema being more common in the older patients. Overall, this does not show worse adverse events in the older age group.

FDA Table 53. FDA analysis of TEAE's by age < 65 or ≥ 65 with a risk difference ≥ 10% between ages groups in key safety population of Study KO-MEN-001

TEAEs	Age < 65 Grade 1-5 N = 42	Age < 65 Grade 3-4 N = 42	Age ≥ 65 Grade 1-5 N = 70	Age ≥ 65 Grade 3-4 N = 70	Risk Difference (Grade 1-5)
Any TEAE	42 (100)	32 (76)	70 (100)	46 (66)	0.00
Haemorrhage (GT)	13 (31)	3 (7)	29 (41)	6 (9)	-10.00
Pruritus	15 (36)	0	11 (16)	0	20.00
Oedema (GT)	9 (21)	1 (2.4)	24 (34)	2 (2.9)	-13.00
Pyrexia	13 (31)	3 (7)	6 (9)	1 (1.4)	22.00
Leukocytosis (GT)	11 (26)	3 (7)	7 (10)	3 (4.3)	16.00
Abdominal pain (GT)	9 (21)	1 (2.4)	7 (10)	0	11.00
Weight decreased	8 (19)	0	5 (7)	0	12.00

Source: FDA analysis of *adae.xpt* and *adsl.xpt*

TEAEs by Race and Ethnicity

Analysis of TEAEs by race and ethnicity is challenging due to the small number of patients in each category present in the key safety population. To investigate any large variations by race, patients were broken down by white (n=88) versus non-white (n=24); the rates of TEAEs in the key safety population were then analyzed with a focus of a risk difference greater than 10 between groupings (FDA Table 54). Overall events were similar between white patients and all others, and no clear signal for safety difference was observed between groupings.

FDA Table 54. FDA analysis of TEAE's by race (white vs pooled other due to small numbers in other race groups) with a risk difference ≥ 10% between groups in key safety population of Study KO-MEN-001

	Non-White Grade 1-5 N = 24	Non-White Grade 3-4 N = 24	White Grade 1-5 N = 88	White Grade 3-4 N = 88	Risk Difference (Grade 1-5)
Any TEAE	24 (100)	17 (71)	88 (100)	61 (69)	0.00
Musculoskeletal pain (GT)	9 (38)	0	22 (25)	4 (4.5)	13.00
Pyrexia	8 (33)	0	11 (13)	4 (4.5)	20.00
Dyspnoea (GT)	7 (29)	1 (4.2)	13 (15)	3 (3.4)	14.00
Febrile neutropenia	2 (8)	2 (8)	23 (26)	23 (26)	-18.00
Decreased appetite	6 (25)	0	13 (15)	1 (1.1)	10.00

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Leukocytosis (GT)	6 (25)	2 (8)	12 (14)	4 (4.5)	11.00
Viral infection (GT)	2 (8)	1 (4.2)	16 (18)	5 (6)	-10.00
Source: FDA analysis of adae.xpt and adsl.xpt					

To investigate any large variations by ethnicity, patients were broken down by participants identifying as non-Hispanic (n=87) versus all other selections (n=25) and the rates of TEAEs in the key safety population were analyzed with a focus of a risk difference greater than 10 between groupings (FDA Table 55). Overall events were similar between non-Hispanics and all others and no clear signal for safety difference was observed between groupings.

FDA Table 55. FDA analysis of TEAE's by ethnicity (not Hispanic vs pooled other due to small numbers in other ethnic groups) with a risk difference $\geq 10\%$ between groups in key safety population of Study KO-MEN-001

TEAEs	All Other Grade 1-5 N = 25	All Other Grade 3-4 N = 25	Non-Hispanic Grade 1-5 N = 87	Non-Hispanic Grade 3-4 N = 87	Risk Difference (Grade 1-5)
Any TEAE	25 (100)	19 (76)	87 (100)	59 (68)	0.01
Nausea (GT)	12 (48)	2 (8)	27 (31)	0	17.00
Dyspnoea (GT)	9 (36)	2 (8)	11 (13)	2 (2.3)	23.00
Decreased appetite	7 (28)	0	12 (14)	1 (1.1)	14.00
Febrile neutropenia	3 (12)	3 (12)	22 (25)	22 (25)	-13.00
Leukocytosis (GT)	6 (24)	2 (8)	12 (14)	4 (4.6)	10.00
Fall	6 (24)	1 (4)	5 (6)	1 (1.1)	18.00
Hypotension (GT)	2 (8)	1 (4)	16 (18)	3 (3.4)	-10.00
Headache (GT)	4 (16)	1 (4)	5 (6)	0	10.00
Source: FDA analysis using adae.xpt, adsl.xpt from SDN 0015 data cut March 21, 2025					

Drug-Disease Interactions

Almost all patients enrolled on ziftomenib trials in the ISS were diagnosed with either relapsed/refractory AML or untreated AML. Only 5 patients were treated with ALL into KO-MEN-001 SS1. Therefore, there is insufficient experience outside of AML to comment on potential drug-disease interactions.

Drug-Drug Interactions

See discussion of drug-drug interactions in Section 6.

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Dose-Dependency for Adverse Events

FDA looked at the most common TEAEs by dose level in the table below (FDA Table 56). Of note, columns for dose levels of 50 mg, 100 mg, and 1000 mg QD were not included since only 1 patient was treated at each of those dose levels. However, those patients are still included in the overall tabulations (n=175). Any grade TEAEs occurred in 100% of patients at all dose levels. There was a lower rate of grade 3-4 TEAEs in the 200 mg QD dose level compared to higher dose levels, which could be interpreted as a dose-dependent effect. However, this observation is confounded by the duration of treatment, as there was a shorter median duration in the 200 mg and 400 mg QD cohorts (31 and 28 days) versus the 600 mg QD (67 days) cohort of patients, in addition to the small sample size of patients treated at doses < 600 mg daily. Interestingly, DS appeared to have similar rates of occurrence in this analysis. However, as noted above, the different genetic makeup of the 200 mg versus 600 mg cohort confounds this analysis since participants with *KMT2A-r* AML made up high proportion of the 200 mg cohort and had a higher rate of DS occurrence. Lastly, QTc prolongation was only reported in the 600 mg cohort. It is unclear if this represents a dose effect with too few patients treated at the 800 mg or 1000 mg dose level to observe this adverse reaction or due to some other factor.

FDA Table 56. KO-MEN-001 TEAEs by Dose Level

Grade	200 mg N = 23		400 mg N = 5		600 mg N = 133		800 mg N = 11		Overall N = 175	
	1-5	3-4	1-5	3-4	1-5	3-4	1-5	3-4	1-5	3-4
Any TEAE	23 (100)	10 (43)	5 (100)	4 (80)	132 (99)	93 (70)	11 (100)	8 (73)	174 (99)	117 (67)
Infection (GT)	11 (48)	7 (30)	1 (20)	1 (20)	64 (48)	35 (26)	8 (73)	4 (36)	85 (49)	48 (27)
Haemorrhage (GT)	9 (39)	1 (4.3)	2 (40)	2 (40)	49 (37)	12 (9)	2 (18)	1 (9)	62 (35)	16 (9)
Nausea (GT)	6 (26)	0	1 (20)	0	47 (35)	2 (1.5)	3 (27)	0	58 (33)	2 (1.1)
Diarrhoea (GT)	7 (30)	0	2 (40)	0	45 (34)	6 (4.5)	3 (27)	0	57 (33)	6 (3.4)
Fatigue (GT)	5 (22)	1 (4.3)	3 (60)	0	44 (33)	11 (8)	1 (9)	1 (9)	55 (31)	13 (7)
Oedema (GT)	8 (35)	0	2 (40)	0	38 (29)	3 (2.3)	2 (18)	0	51 (29)	3 (1.7)
Musculoskeletal pain (GT)	8 (35)	0	1 (20)	0	35 (26)	4 (3)	3 (27)	0	48 (27)	4 (2.3)
Bacterial infection (GT)	4 (17)	3 (13)	1 (20)	0	35 (26)	21 (16)	1 (9)	1 (9)	42 (24)	25 (14)
Hypokalaemia	5 (22)	2 (9)	0	0	33 (25)	14 (11)	1 (9)	0	40 (23)	16 (9)
Anaemia	7 (30)	7 (30)	1 (20)	1 (20)	31 (23)	29 (22)	1 (9)	1 (9)	40 (23)	38 (22)
Differentiation syndrome	7 (30)	4 (17)	0	0	36 (27)	19 (14)	0	0	44 (25)	24 (14)
Transaminases increased (GT)	5 (22)	3 (13)	1 (20)	1 (20)	29 (22)	12 (9)	2 (18)	0	38 (22)	16 (9)

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Febrile neutropenia	7 (30)	7 (30)	1 (20)	1 (20)	30 (23)	29 (22)	1 (9)	1 (9)	39 (22)	38 (22)
Renal impairment (GT)	4 (17)	1 (4.3)	2 (40)	1 (20)	25 (19)	7 (5)	4 (36)	1 (9)	37 (21)	10 (6)
Dyspnoea (GT)	6 (26)	1 (4.3)	0	0	28 (21)	5 (3.8)	2 (18)	0	36 (21)	6 (3.4)
Leukocytosis (GT)	5 (22)	2 (9)	1 (20)	0	24 (18)	9 (7)	1 (9)	1 (9)	31 (18)	12 (7)
Thrombocytopenia	4 (17)	3 (13)	1 (20)	1 (20)	24 (18)	24 (18)	1 (9)	1 (9)	30 (17)	29 (17)
Platelet count decreased	3 (13)	3 (13)	0	0	17 (13)	17 (13)	0	0	20 (11)	20 (11)
Neutropenia	2 (9)	2 (9)	0	0	15 (11)	15 (11)	2 (18)	2 (18)	20 (11)	20 (11)
Hyperglycaemia	1 (4.3)	0	1 (20)	0	16 (12)	12 (9)	0	0	18 (10)	12 (7)
Hypoxia	3 (13)	3 (13)	1 (20)	0	13 (10)	9 (7)	0	0	17 (10)	12 (7)
Electrocardiogram QT prolonged	0	0	0	0	14 (11)	9 (7)	0	0	14 (8)	9 (5)
White blood cell count decreased	3 (13)	1 (4.3)	0	0	9 (7)	7 (5)	1 (9)	1 (9)	13 (7)	9 (5)
Neutrophil count decreased	3 (13)	3 (13)	0	0	5 (3.8)	5 (3.8)	1 (9)	1 (9)	9 (5)	9 (5)

Source: FDA analysis using *adae.xpt*, *adsl.xpt* from SDN 0015 data cut March 21, 2025

GT indicates FDA grouped term

8.3.8. Specific Safety Studies/Clinical Trials

No specific safety studies were submitted.

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

An analysis of the SOC “Neoplasms benign, malignant, and unspecified (including cysts and polyps)” revealed the following secondary malignancies in participants enrolled in KO-MEN-001:

- Subject ^{(b) (6)} Benign bone neoplasm
- Subject ^{(b) (6)} Benign breast neoplasm and gastrointestinal neoplasm.
 - Subject had past medical history of gastrointestinal neoplasm.

Given the short median exposure of ziftomenib, the single-arm study design, and the extensive past cancer treatments for this population with R/R AML, it is not possible to attribute these events to ziftomenib. However, the review team notes that lymphoma did occur in a mouse during the 13-week toxicity study (see Section 5), and as such, this information is disclosed in Section 13.1 of the ziftomenib USPI.

Human Reproduction and Pregnancy

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Effects of ziftomenib on human reproduction and pregnancy were not evaluated in this application.

Pediatric and Assessment of Effects on Growth

Study KO-MEN-001 did not enroll pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Ziftomenib does not have significant risk of abuse. No withdrawal or rebound effects have been identified.

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

FDA agrees with the Applicant that this is not applicable since ziftomenib is not approved or marketed for commercial use in any country.

Expectations on Safety in the Postmarket Setting

FDA agrees with the Applicant that the expected safety profile in the postmarket setting is anticipated to be similar to that observed in clinical trials.

8.3.11. Integrated Assessment of Safety

The FDA's analysis of safety event rates differed with the Applicant's because of the use of FDA derived group terms as detailed in FDA Table 69 and FDA Table 70. FDA also disagreed with Applicant's root cause of deaths that occurred within 30 days of treatment as noted above. The overall safety profile for ziftomenib based on FDA analysis of clinical trials is summarized in FDA Table 57 below.

FDA Table 57. Safety summary of the pivotal study KO-MEN-001 and the pooled population from the ISS.

	KO-MEN-001	KO-MEN-001	ISS
	<i>NPM1m</i>	<i>All safety</i>	<i>Ziftomenib treated</i>
	N = 112	N = 175	N = 353
	n (%)	n (%)	n (%)
Total Deaths	84 (75)	130 (74)	200 (57)
On-treatment deaths*	42 (37.5)	74 (42)	110 (31)
TEAEs leading to death	27 (24)	44 (25)	62 (17)

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All-Grade TEAEs	112 (100)	174 (99)	354 (99)
Grade 3-5 TEAEs	105 (94)	161 (92)	330 (93)
SAEs	89 (79)	140 (80)	270 (76)
All-Cause Discontinuation	107 (96)	170 (97)	296 (84)
TEAEs with discontinuation	24 (21)	38 (22)	53 (15)
* Indicates death that occurred within 30 days of treatment			
Source: FDA analysis using adae.xpt, adsl.xpt from SDN 0015 data cut March 21, 2025			

Total deaths were higher in Study KO-MEN-001 versus the ISS population of pooled studies, which is reflective of the ISS population containing 76 newly diagnosed patients enrolled to Study KO-MEN-007 and the preliminary nature of the follow-up data for Studies KO-MEN-007 and KO-MEN-008. On-treatment deaths and grade 5 TEAEs were similar but slightly higher on KO-MEN-001 versus ISS, again for reasons mentioned for total deaths. The high rates of all-grade TEAEs, grade 3-5 TEAEs, SAEs, and all-cause discontinuation reflect the high background rates of adverse events in patients with active AML with most patients (277/353) in the ISS pool and all participants enrolled on KO-MEN-001 having R/R AML. Despite this high background rate of TEAEs, the observation that only 15-22% of patients across the studies had TEAEs leading to discontinuation suggests that most toxicity observed was attributed to the disease or expected complications of active AML and not to study treatment.

The safety profile of the most common TEAEs in Study KO-MEN-001 were generally consistent with those that occur in AML patients with active disease and consistent in the safety subset of NPM1m patients and the ISS population (FDA Table 58). The general categories for common TEAEs often observed in active AML included infections, cytopenias, bleeding events, and GI toxicity. TEAEs that are not associated with AML itself and induced or likely worsened by ziftomenib treatment were differentiation syndrome and QT prolongation.

FDA Table 58. FDA analysis of common TEAEs across KO-MEN-001 and ISS population.

	KO-MEN-001				ISS	
	NPM1m 600 mg qd		All patients		All Patients in ISS	
Ziftomenib therapy	monotherapy				mono and combo therapy	
TEAEs	Grade 1-5 N = 112	Grade 3-4 N = 112	Grade 1-5 N = 175	Grade 3-4 N = 175	Grade 1-5 N = 353	Grade 3-4 N = 353
Any TEAE	112 (100)	78 (70)	174 (99)	117 (67)	351 (99)	265 (75)
Infection (GT)	58 (52)	31 (28)	85 (49)	48 (27)	170 (48)	103 (29)
Haemorrhage (GT)	42 (38)	9 (8)	62 (35)	16 (9)	134 (38)	25 (7)
Diarrhoea (GT)	40 (36)	6 (5)	57 (33)	6 (3.4)	145 (41)	20 (6)
Nausea (GT)	39 (35)	2 (1.8)	58 (33)	2 (1.1)	142 (40)	10 (2.8)
Fatigue (GT)	38 (34)	9 (8)	55 (31)	13 (7)	114 (32)	28 (8)

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Oedema (GT)	33 (29)	3 (2.7)	51 (29)	3 (1.7)	102 (29)	7 (2)
Bacterial infection (GT)	31 (28)	17 (15)	42 (24)	25 (14)	91 (26)	42 (12)
Musculoskeletal pain (GT)	31 (28)	4 (3.6)	48 (27)	4 (2.3)	110 (31)	10 (2.8)
Hypokalaemia	29 (26)	13 (12)	40 (23)	16 (9)	96 (27)	29 (8)
Differentiation syndrome	29 (26)	15 (13)	44 (25)	24 (14)	58 (16)	31 (9)
Pruritus	26 (23)	0	32 (18)	0	72 (20)	9 (2.5)
Febrile neutropenia	25 (22)	25 (22)	39 (22)	38 (22)	122 (35)	117 (33)
Anaemia	25 (22)	23 (21)	40 (23)	38 (22)	94 (27)	86 (24)
Transaminases increased (GT)	23 (21)	9 (8)	38 (22)	16 (9)	91 (26)	32 (9)
Thrombocytopenia	22 (20)	22 (20)	30 (17)	29 (17)	39 (11)	37 (10)
Renal impairment (GT)	21 (19)	7 (6)	37 (21)	10 (6)	66 (19)	17 (4.8)
Viral infection (GT)	18 (16)	6 (5)	23 (13)	8 (4.6)	45 (13)	13 (3.7)
Leukocytosis (GT)	18 (16)	6 (5)	31 (18)	12 (7)	43 (12)	16 (4.5)
Platelet count decreased	15 (13)	15 (13)	20 (11)	20 (11)	93 (26)	90 (25)
Hyperglycaemia	14 (13)	10 (9)	18 (10)	12 (7)	40 (11)	25 (7)
Neutropenia	15 (13)	15 (13)	20 (11)	20 (11)	25 (7)	25 (7)
Electrocardiogram QT prolonged	13 (12)	9 (8)	14 (8)	9 (5)	27 (8)	18 (5)
Hypertension (GT)	12 (11)	6 (5)	14 (8)	6 (3.4)	27 (8)	15 (4.2)
Hypoxia	10 (9)	6 (5)	17 (10)	12 (7)	37 (10)	24 (7)
White blood cell count decreased	8 (7)	7 (6)	13 (7)	9 (5)	52 (15)	48 (14)

Source: FDA analysis using *adae.xpt*, *adsl.xpt* from SDN 0015 data cut March 30, 2025

Differentiation syndrome emerged as a notable adverse event across ziftomenib clinical studies, with incidence varying by genetic subtype and dose. In the KO-MEN-001 study focusing on patients with *NPM1*-mutated AML receiving 600 mg daily monotherapy, DS occurred in 27 patients (24%) with any grade severity, with 15 patients (13%) experiencing grade 3-4 events. When examining genetic subtypes, patients with *KMT2A-r* demonstrated a higher overall incidence of DS (42%, 15/36 patients) compared to patients with *NPM1-m* (24%, 29/120 patients), while no cases were observed in the "Other" genetic subtype group (0/16 patients). The severity distribution showed that most cases were grades 1-3, with patients with *KMT2A-r* experiencing 11% grade 5 events (4/36) compared to only 2% (2/120) in patients with *NPM1-m*. Across the broader ISS, including participants who received both monotherapy and combination therapy (n=353), DS occurred in 55 participants (16%) at any grade and 31 participants (9%) at grade 3-4, suggesting this AR represents a manageable but clinically significant consideration in ziftomenib treatment. The rate of DS was similar between the key safety population and the overall KO-MEN-001 population but was lower in the ISS population, due to lower rates of reported DS in combination therapy studies KO-MEN-007 and KO-MEN-008 (6%, 10/168

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patients). As noted above, the all-grade rate of DS in KO-MEN-001 was higher in the population with a *KMT2A*-r compared to the population with an *NPM1*-m (42% vs 24%, respectively).

Ultimately, the frequency and potential severity of DS with ziftomenib monotherapy use led the Applicant to propose a boxed warning for DS. The FDA agreed with this recommendation and ensured that the warning and precaution for DS described the trial experience for the labeled patient population of adult patients with R/R AML with a susceptible *NPM1*-m, as well as the higher rate and severity of DS in patients with *KMT2A*-r acute leukemia to fully inform treating physicians (see Section 11).

QTc prolongation also occurred with ziftomenib treatment and was not caused by active AML. The FDA analysis identified that the rate of any QT prolongation in the key safety population was 12% (13/112). Moreover, 8% (9/112) of the key safety population had grade 3 events with QTc prolongation of either > 60ms from baseline or a QTc > 500ms. There were no grade 4 or 5 events reported. The rate of QTc prolongation was lower in the overall KO-MEN-001 and ISS populations at 8% all grade and 5% grade 3 in both. Due to the single arm nature of these studies, it is difficult to account for the confounding effects of concomitant medications that are also known to increase the QTc interval. However, the FDA analysis of ziftomenib concentration versus Δ QTc combined with the potential for ziftomenib concentration boosting from drug-drug interactions and food effects combined with the observed AE rate, led FDA to add a warning and precautions for QTc prolongation to the ziftomenib label.

With these additional mitigation strategies, the FDA agrees with the Applicant that based on the totality of efficacy and safety data, the benefit/risk profile of ziftomenib in the treatment of patients with R/R AML with a susceptible *NPM1* mutation who have no satisfactory alternative treatment options is favorable.

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SUMMARY AND CONCLUSIONS

8.4. Statistical Issues

The FDA's Assessment:

Study KO-MEN-001 demonstrated a numerically higher than historically reported response rate in adult participants with R/R AML with an *NPM1* mutation. The CR + CRh rate was 21.4% (95% CI: 14.2%, 30.2%) in the Pooled Efficacy Cohort and 18.5% (95% CI: 11.1%, 27.9%) in its Phase 2 subset (pivotal cohort). The lower bound of 95% CI of the Phase 2 cohort did not exclude the prespecified benchmark of 12% based on the FDA's adjudication; however, the response of Phase 2 patients based on Applicant's assessments as well as the Pooled Efficacy Cohort did exclude this benchmark. The median duration of response was 5.0 (95% CI: 1.9, 8.1) months, and the rate of conversion to transfusion independence was 21.2% (95% CI: 12.1%, 33.0%) in Pooled Efficacy Cohort.

One issue identified during the FDA's review of response data was that there was no pre-specification of a time window between the marrow sampling and the CBC for remission assessment. As a result, some patients did not have marrow sampling in adjunction with CBC assessment to support the adjudication of remission after clearance of bone marrow blasts, at which point participants stopped monthly marrow assessments. For the adjudication process for this application, we used a window of -7 to +14 days along, in addition to clinical judgement. While the initial results excluded the benchmark rate of 12%, the adjudicated results did not. This raises questions about the robustness of the results.

Another change in the FDA's efficacy analysis from what was specified in the SAP was to establish the effectiveness on the pooled population of Phase 1 and 2. This pooling was supported by the same eligibility criteria used in two phases and the similarity of two study populations in terms of baseline characteristics. The pooled results appeared to confirm the initial inference based on the Applicant's assessments for Phase 2 patients only. The FDA evaluated the impact of borrowing from Phase 1 data by Bayesian analysis under various effective sample size assumptions. These results suggested that the probability to exceed the benchmark rate was over 97.5% as long as the Phase 1 data were considered at least relevant enough to borrow half of the formation.

8.5. Conclusions and Recommendations

The FDA's Assessment:

The clinical benefit of ziftomenib in KO-MEN-001 was established based on a CR + CRh rate of 21.4% (95% CI: 14.2%, 30.2%) in adult participants with R/R AML with an *NPM1* mutation identified by local testing. The median DoR was 5.0 months. However, the rate of conversion from transfusion-dependence to transfusion-independence did not confer a significant benefit (21.2%). In addition, the median duration of treatment was only 2.2 months, with only 16% of

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participants receiving ziftomenib for > 6 months. However, the short-term benefits of ziftomenib are considered to be meaningful.

Ziftomenib was generally well-tolerated, with toxicities that were manageable by dose interruption. Serious risks include differentiation syndrome and QTc prolongation, which are mitigated by appropriate labeling. Fatal adverse reactions included DS, infection, and sudden death. However, the long-term safety of ziftomenib has not been established, and requires a postmarketing study. In addition, the short duration of response, modest CR + CRh rate, and low conversion to transfusion independence preclude the use of ziftomenib in the general relapsed or refractory population, who would be better served by cytotoxic chemotherapy or agents targeting other mutations. Therefore, the review team recommend approval for ziftomenib for the treatment of adult patients with relapsed or refractory AML with an *NPM1* mutation who have no satisfactory alternative treatment options.

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9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This application was not discussed at an Advisory Committee meeting. The review of this drug did not raise significant safety issues that were unexpected for the class of drug or for the treatment of patients with R/R AML. In addition, the efficacy appears to be consistent among other drugs in this class.

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10 Pediatrics

The Applicant's Position:

There is currently no data regarding the use of ziftomenib in the pediatric population.

Ziftomenib is directed at inhibiting the menin-MLL(KMT2A) interaction, which is considered a relevant molecular target for the purposes of Section 505B of the Federal Food, Drug, and Cosmetic Act. To comply with the pediatric study requirements in Section 505B(e), an initial pediatric study plan (iPSP) was agreed to on 16 August 2024; a partial waiver for patients <1 month of age and a deferral for patients $\geq$ 1 month of age is included in this submission.

The FDA's Assessment:

Ziftomenib is a molecularly targeted drug for the treatment of a cancer in adults, this application is subject to the FDARA amendment to PREA. Under the agreed iPSP, the Applicant requested a partial waiver for patients < 1 month of age. The Division concurs that the population of patients with R/R acute leukemia < 1 month of age is rare, and that studies would be highly impracticable in this population. The Division agrees with a partial waiver for ziftomenib for patients < 1 month of age.

The Applicant requested a deferral for patients 1 month to < 17 years of age with relapsed or refractory acute leukemia harboring *KMT2A* rearrangements, *NPM1* mutations, and *NUP98* rearrangements, as the study in adult patients was completed. ^{(b) (4)}

The Division agrees with a deferral for this patient population.

The Division's plan was discussed at the OCE-PeRC meeting on September 24, 2025. A postmarketing requirement (PMR) will be included for completion and submission of a final CSR for Study ^{(b) (4)}, as detailed in Section 13, below.

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11 Labeling Recommendations

The Applicant's Position:

This is an original NDA application. The draft proposed label can be found in Module 1.14.1.3.

The FDA's Assessment:

Section	Proposed Labeling	Approved Labeling
Boxed Warning	Included a boxed warning for differentiation syndrome.	FDA agreed.
1 Indications and Usage	Treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a nucleophosmin 1 (<i>NPM1</i>) mutation.	FDA modified to specify that the indication is limited to patients with a susceptible <i>NPM1</i> mutation who have no satisfactory alternative treatment options.
2 Dosage and Administration	In subsection 2.1 Patient Selection, the applicant included statement to select patients based on presence of <i>NPM1</i> mutation with cross reference to Clinical Studies (14). In subsection 2.3 Administration, instructions for how to handle missed dosages of less than 12 hours prior to the next scheduled was not included. In subsection 2.4 Dosage Modifications for (b)(4) included a dosage modification table.	In subsection 2.1 Patient Selection, FDA specified "susceptible <i>NPM1</i> mutation" to align with agreed upon indication statement. FDA added instructions for how a patient should handle a missed dosage discovered less than 12 hour prior to the next dose due. FDA modified Table 1 to include instructions for dose reductions/restarting after dosage interruption. FDA added a dose reduction table 2 to describe first, second, and any further reductions/permanent discontinuation instructions. FDA added a new subsection 2.4 for dosage modifications for concomitant use of acid-reducing agents.
5 Warnings and Precautions (W&P)	Included W&P for differentiation syndrome. Included W&P for embryo-fetal toxicity.	FDA agreed but made minor edits to remove statements of negative data and add missing cross-reference. The rate of differentiation syndrome were

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		updated to reflect the adjudicated rate of DS in KO-MEN-001. FDA added QTc Interval Prolongation as a new Warning and Precaution
6 Adverse Reactions	Included data from study KO-MEN-001.	FDA generally agreed but modified the section to remove any statements of negative data, add missing fatalities, and to align formatting with other recent labels in oncology.
7 Drug Interactions	In subsection 7.1, Effect of Other Drugs on KOMZIFTI, included data on strong or moderate CYP3A4 inducers and inhibitors and gastric reducing agents. (b) (4) (b) (4) (b) (4) Other Drugs, included that ziftomenib has no impact on exposure of sensitive (b) (4) UGT1A1 substrates and that KOMZIFTI can be coadministered with these agents.	FDA modified data concerning strong and moderate CYP3A4 inhibitors to include the potential for increased risk of QTc prolongation. (b) (4) FDA updated the ARA section to describe use of ziftomenib with gastric acid reducing agents. FDA added language regarding on avoiding concomitant use of drugs that prolong the QTc interval. (b) (4)
8 Use in Specific Populations	Included subsections 8.1-8.7	FDA generally agreed with the applicant but made some modifications for alignment with other drugs in the class/oncology, as well as for clarity. In subsection 8.5 Geriatric Use, FDA updated numbers to include all patients who received the recommended dosage.
12 Clinical Pharmacology	Included subsections 12.1 Mechanism of Action, subsection 12.2 Pharmacodynamics, and subsection 12.3 Pharmacokinetics	FDA revised subsection 12.1 Mechanism of Action to remove promotional language, in addition to removing statements not supported by data submitted to the FDA.

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		FDA modified subsection 12.2 to update the risk of QTc prolongation with ziftomenib treatment. FDA modified subsection 12.3 to include the PK table describing PK parameters with and without food and to update the results of Drug Interaction Studies.
14 Clinical Studies	Included ^(b) ₍₄₎ patients in efficacy population. Efficacy endpoints include CR/CRh rates, duration of CR/CRh, rate of conversion from transfusion dependence to independence, and median follow-up.	FDA agreed with efficacy endpoints described but modified the section to include the full population of patients with AML with an <i>NPM1</i>m (n=112) who received the recommended dosage because this full population is relevant to interpreting the efficacy data from KOMEN-101. FDA simplified the demographics and disease characteristics table for brevity and clarity.
Medication Guide	Included a Medication Guide	Medication Guide modified by FDA to align with changes made to the full prescribing information.*
<i>*See review from the patient labeling team within DMPP archived separately in DARRTS for further details.</i>		

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12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

Based on this review, a REMS is not necessary to ensure that the benefits outweigh the risks of ziftomenib for the treatment of adult patients with relapsed or refractory AML harboring a susceptible *NPM1* mutation who have no satisfactory alternative treatment options. The management of the risks associated with ziftomenib treatment, including differentiation syndrome and QTc prolongation, will be communicated through labeling.

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13 Postmarketing Requirements and Commitment

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
X	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	No
X	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	No
X	Other considerations (e.g.: PK/PD), if applicable:	Yes

Recommended Postmarketing Requirements

1. PMR #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.
2. PMR #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.
3. PMR #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."
4. PMR #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."

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Version date: March 1, 2024 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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5. PMR #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.
6. PMR #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.
7. PMR #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 excess drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled M12 Drug Interaction Studies.

Recommended Postmarketing Commitments

1. PMC #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.
2. PMC #4929-9: Conduct an *in vitro* study to clarify the active of ziftomenib in acute myeloid leukemia cells with *NPM1* mutations other than the A, B, and D subtypes.

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14 Appendices

14.1. References

The Applicant's References:

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The FDA's References:

See footnotes throughout.

14.2. **Financial Disclosure**

The Applicant's Position:

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Covered Clinical Study (Name and/or Number): KO-MEN-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>632</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in study: <u>N/A</u> Sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>9</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

The FDA confirms that this information is correct. Financial Certification and Disclosure information is found in Section 1.3.4 of SDN001.

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14.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

There are no additional nonclinical pharmacology/toxicology analyses.

The FDA's Assessment:

The FDA agrees that there are no additional nonclinical pharmacology/toxicology analyses.

14.4. OCP Appendices (Technical documents supporting OCP recommendations)

14.4.1. Bioanalytical Methods

The validation methods for ziftomenib are outlined in FDA Table 59.

FDA Table 59. Summary of Method Performance for the Determination of Ziftomenib, KO-516, and KO-739 in Plasma (BTM-2812-R0)

METHOD VALIDATION	
Method description	
Bioanalytical method validation report name, amendments	Report for the Validation of Method ^{(b) (4)} -2812: Determination of KO-539 and its Metabolites KO-516, KO-739 in Human Plasma (K2EDTA) by LC-MS/MS Method Validation Report 934-R9876 Addendum 934-R9876A1
Method description	Method ^{(b) (4)} -2812-R0 is an LC-MS/MS method for the determination of ziftomenib and its metabolites, KO-516 and KO-739, in K2EDTA human plasma using KO-747 as the internal standard. Ziftomenib, KO-516, KO-739, and its internal standard were extracted from human plasma through protein precipitation using acetonitrile. Reversed-phase HPLC separation of the analytes was achieved with a Waters XBridge C18 column (50 × 2.1 mm, 3.5 micron). MS/MS detection was set at mass transitions of m/z 718.3→191.2 for ziftomenib, m/z 704.3→191.2 for KO-516, m/z 734.3→191.2 for KO-739, and m/z 726.3→192.2 for KO-747 (IS) in TIS positive mode.
Materials used for standard calibration curve and concentration	Ziftomenib, Batch PS02684-20-E-P1, ^{(b) (4)} Calibration standards: 0.200, 0.400, 2.00, 10.0, 40.0, 80.0, 160, and 200 ng/mL (ULOQ) KO-516, Lot 04A, Kura Oncology Stock solution: 15,000 ng/mL KO-739, Lot 02A, Kura Oncology Stock solution: 15,000 ng/mL Internal standard: KO-747 (deuterated ziftomenib), Lot 01A, Kura Oncology
Validated assay range	0.200 to 200 ng/mL
Material used for QCs and concentration	Ziftomenib, Batch PS02684-20-E-P1, ^{(b) (4)} QC concentrations: 0.200 (LLOQ), 0.600, 60.0, 150, and 15,000 ng/mL (Dilution QC) Internal standard: KO-747 (deuterated ziftomenib), Lot 01A, Kura Oncology

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Minimum required dilutions	NR		
Source and lot of reagents	Blank K2EDTA human plasma, ^{(b) (4)} Lot numbers HMN16551 through HMN16556 K2EDTA human whole blood ^{(b) (4)} Lot number HMN36167 High lipemic human plasma Lot number BRH1541889		
Regression model and weighting	Linear, weighted (1/x ²)		
Method validation summary			Acceptability
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	
	Cumulative accuracy (%bias) from LLOQ to ULOQ	Ziftomenib: -3.0% to 4.0% KO-516: -4.5% to 2.0% KO-739: -1.3% to 1.5%	
	Cumulative precision (%CV) from LLOQ to ULOQ	Ziftomenib: ≤6.2% KO-516: ≤8.7% KO-739: ≤10.1%	
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QC levels	Ziftomenib: 0.0% to 6.2% KO-516: -3.5% to 5.3% KO-739: -2.0% to 3.7%	
	Inter-run % CV	Ziftomenib: ≤11.1% KO-516: ≤12.6% KO-739: ≤13.4%	
	Total error	NR	
Selectivity and matrix effect	Selectivity for ziftomenib was considered acceptable in 6 lots of plasma tested. Interlot accuracy and precision at 0.600 and 150 ng/mL, mean matrix factor (%CV) of 6 lots of plasma: Ziftomenib: 1.07 (4.7%) to 1.04 (2.9%) KO-516: 0.98 (5.1%) to 1.07 (2.8%) KO-739: 0.92 (8.7%) to 1.08 (8.3%)		Yes
Interference and specificity	No significant chromatographic interferences were detected from the analyte onto its IS.		Yes
Hemolysis effect	No significant effect of 2% hemolyzed plasma at 0.600 and 150 ng/mL: Ziftomenib Accuracy (%bias): -2.7% to 1.3% Precision (%CV): ≤5.8% KO-516: Accuracy (%bias): -8.5% to -7.3% Precision (%CV): ≤7.8% KO-739: Accuracy (%bias): -7.3% to -2.0% Precision (%CV): ≤8.5%		Yes

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Lipemic effect	No significant effect of lipemia at 0.600 and 150 ng/mL: Ziftomenib: Accuracy (%bias): -1.7% to 0.7% Precision (%CV): ≤4.1% KO-516: Accuracy (%bias): -4.5% to -0.7.% Precision (%CV): ≤8.6% KO-739: Accuracy (%bias): -10.3% to -4.0% Precision (%CV): ≤11.4%	Yes
Dilution linearity and hook effect	Dilution factor up to 100-fold of 15000 ng/mL for all analytes Ziftomenib: Accuracy (%bias): 2.0% Precision (%CV): 1.0% KO-516: Accuracy (%bias): 4.0% Precision (%CV): 1.6% KO-739: Accuracy (%bias): 1.3% Precision (%CV): 2.3% Hook effect: NA	Yes
Bench-top/process stability	22.5 hr in plasma at room temperature for bench-top samples 73.0 hr at room temperature for processed samples	Yes
Freeze-thaw stability	5 cycles at -70°C and -20°C	Yes
Long-term storage	378 days at -70°C and -20°C	Yes
Parallelism	NR	NA
Carryover	Carryover was evaluated during each validation run by injecting at least 1 double blank after the ULOQ standard. There was no significant carryover evident in the blanks injected directly after the ULOQ standard samples.	Yes
IN-USE PERFORMANCE, KO-MEN-001 (Bioanalytical Report: KO-BA-0206)		
Assay passing rate	Ziftomenib: 73 of 75 runs (97.3%) met acceptance criteria KO-516: 71 of 75 runs (94.7%) met acceptance criteria KO-739: 70 of 75 runs (96.0%) met acceptance criteria	Yes
Standard curve performance	Ziftomenib: Cumulative accuracy (%bias): -2.0% to 2.0% Cumulative precision (%CV): ≤6.9% KO-516: Cumulative accuracy (%bias): -0.6% to 1.0% Cumulative precision (%CV): ≤7.7% KO-739: Cumulative accuracy (%bias): -1.5% to 1.0% Cumulative precision (%CV): ≤7.8%	Yes

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	Total error: NR	
QC performance	Ziftomenib: Cumulative accuracy (%bias): -2.0% to -0.5% Cumulative precision (%CV): ≤9.9% Total error: NR KO-516: Cumulative accuracy (%bias): -1.8% to 0% Cumulative precision (%CV): ≤11.1% Total error: NR KO-739: Cumulative accuracy (%bias): -2.7% to -1.3% Cumulative precision (%CV): ≤9.2% Total error: NR	Yes
Method reproducibility	Of 150 samples reanalyzed to test the reproducibility of the method for ziftomenib, 98% of the ISR results had a relative %difference within the acceptance criteria (±20%). Of 150 samples reanalyzed to test the reproducibility of the method for KO-516, 81.3% of the ISR results had a relative %difference within the acceptance criteria (±20%). Of 150 samples reanalyzed to test the reproducibility of the method for KO-739, 86.7% of the ISR results had a relative %difference within the acceptance criteria (±20%).	Yes
Study sample analysis stability	Approximately 98% of the PK samples were analyzed within the established stability window (378 days). Approximately 2% of samples were analyzed outside the window. More than half were due to re-assay.	Yes
Standard calibration curve performance during accuracy and precision	Ziftomenib: 71 calibrator sets of 2 replicates each of 8 concentration levels from 0.200 to 200 ng/mL (total 1136 datapoints) – 52 datapoints rejected KO-516: 65 calibrator sets of 2 replicates each of 8 concentration levels from 0.200 to 200 ng/mL (total 1040 datapoints) – 118 datapoints rejected KO-739: 70 calibrator sets of 2 replicates each of 8 concentration levels from 0.200 to 200 ng/mL (total 1120 datapoints) – 139 datapoints rejected	

14.4.2. Population PK Analysis

14.4.2.1. Executive Summary

The FDA's Assessment:

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In general, the applicant's population PK (PopPK) analysis is considered acceptable for the purpose of characterizing the PK profile of ziftomenib and its metabolites KO-516 and KO-739 in adult patients with R/R AML. There is no clinical meaningful impact for covariates including body weight, sex, race, age (18-86 years old), renal and hepatic impairment (mild or moderate), and p-gp inhibition. Based on simulation, fed status and strong CYP3A4 inhibitors can cause ~6 and ~2-fold increase in exposure, respectively. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

14.4.2.2. PPK Assessment Summary

The Applicant's Position:

General Information	
Objectives of PPK Analysis	- To develop a PPK model for ziftomenib, and metabolites KO-516 and KO-739 - To identify the source of variability and elucidate the effects of intrinsic and extrinsic factors on ziftomenib PK parameters - Predict ziftomenib exposure for E-R assessment
Study Included	KO-MEN-001 and KO-MEN-003
Dose(s) Included	50 mg – 1000 mg
Population Included	Healthy adults, adult patients with R/R AML
Population Characteristics (Applicant Table 24)	General <u>Age</u> : median 64.5 years (range: 18-86 years) <u>Weight</u> : median: 71.5 kg (range: 41-135 kg) <u>Sex</u> : 92 (48.9%) male, 96 (51.1%) female <u>Race</u> : White, 141 (75%); Asian, 6 (3.2%); Black or African American, 10 (5.3%); Missing, 27 (14.4%); Other, 4 (2.1%)
	Organ Impairment Hepatic (NCI-ODWG): Normal, 137 (78.7%); Mild, 32 (18.4%); Moderate, 5 (2.9%) Renal (eGFR): Normal, 73 (42%); Mild, 66 (37.9%); Moderate, 21 (12.1%); Missing, 14 (8%)
	Pediatrics (if any) None.
No. of Patients, PK Samples, and BLQ	2436 measurable plasma concentrations of ziftomenib, 2376 measurable plasma concentrations KO-739 and 2299 measurable plasma concentrations KO-516, from 188 subjects (14 healthy volunteers and 174 patients with R/R AML)

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Sampling Schedule	Rich Sampling	Parts 1a and 1b of KO-MEN-001: Pre-dose, and 0.5, 1, 2, 3, 4, 6, 8, 24 hours post dose (on cycle 1 day 1 and cycle 2 day 1) KO-MEN-003: Pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 hours post dose
	In ITT Population	1-2, 3-4, 5-8, 20-26 hours post dose (Cycle 1 day 1) Predose, and 1-2, 3-4, 5-8 hours post dose (Cycle 2 day 1) Predose Cycle 3+ day 1
Covariates Evaluated	Static	Applicant Table 24
	Time-varying	Applicant Table 24
Final Model		Summary
		Acceptability [FDA's comments]
Software and Version	NONMEM Version VII (level 7.5) for PPK. Dataset preparation, ER analyses, data exploration, figures and tables were generated using R® V4.4.2 with comprehensive R archive network (CRAN) and (b) (4).	Adequate
Model Structure	A 2-compartment model first-order elimination, and first-order absorption with a lag time best described ziftomenib PK data. A proportional residual variability model was used.	Adequate
Model Parameter Estimates	Applicant Table 25	Adequate
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Applicant Table 25	Adequate
BLQ for Parameter Accuracy	The total number of PK samples collected after a first ziftomenib dose BLQ represented 1.8% for ziftomenib, 3.8% for KO-739 and 6.7% for KO-516 (i.e., 47/2614 for ziftomenib, 98/2613 for KO-739 and 176/2613 for KO-516). Since less than 10% of postdose concentrations were BLQ following oral dosing, a likelihood method accounting for the probability of BLQ was not implemented due to the low number of post dose BLQ values.	Adequate

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GOF, VPC	Applicant Figure 4 and Applicant Figure 5	Adequate
Significant Covariates and Clinical Relevance	Applicant Figure 6 (forest plot)	Adequate
Analysis Based on Simulation (optional)	The impact of intrinsic and extrinsic factors on ziftomenib PK was analyzed. Refer to KO-PK-0001, Section 12.3.3 and 12.3.4.	Adequate
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	The PK characteristics of ziftomenib are summarized in USPI Section 12.3, pharmacokinetics.	Adequate

Applicant Table 24: Applicant - Summary of Continuous and Categorical Covariates in the Population PK Dataset

Covariates	KO-MEN-001 (N=174)	KO-MEN-003 (N=14)	Total (N=188)
Age (years)			
Mean (SD)	61.5 (15.9)	37.8 (11.2)	59.8 (16.8)
Median [Min, Max]	66.0 [18.0, 86.0]	39.0 [22.0, 55.0]	64.5 [18.0, 86.0]
Weight (kg)			
Mean (SD)	74.5 (18.1)	76.4 (10.2)	74.7 (17.6)
Median [Min, Max]	71.1 [41.0, 135]	76.7 [61.5, 93.0]	71.5 [41.0, 135]
Missing	2 (1.1%)	0 (0%)	2 (1.1%)
Height (cm)			
Mean (SD)	168 (9.72)	172 (10.3)	168 (9.80)
Median [Min, Max]	168 [142, 188]	173 [154, 193]	168 [142, 193]
Missing	12 (6.9%)	0 (0%)	12 (6.4%)
BMI (kg/m²)			
Mean (SD)	26.2 (5.96)	25.7 (1.98)	26.2 (5.75)
Median [Min, Max]	25.4 [14.2, 52.7]	26.0 [21.9, 28.7]	25.5 [14.2, 52.7]
Missing	14 (8.0%)	0 (0%)	14 (7.4%)
BSA (m²)			
Mean (SD)	1.84 (0.235)	1.89 (0.180)	1.84 (0.231)
Median [Min, Max]	1.83 [1.37, 2.46]	1.91 [1.60, 2.24]	1.84 [1.37, 2.46]
Missing	14 (8.0%)	0 (0%)	14 (7.4%)
CrCL (mL/min)			
Mean (SD)	94.9 (44.6)	104 (14.1)	95.6 (43.1)
Median [Min, Max]	85.5 [30.9, 324]	107 [83.4, 133]	88.6 [30.9, 324]

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Covariates	KO-MEN-001 (N=174)	KO-MEN-003 (N=14)	Total (N=188)
Missing	2 (1.1%)	0 (0%)	2 (1.1%)
eGFR (mL/min/1.73m²)			
Mean (SD)	92.1 (37.5)	95.1 (15.4)	92.4 (36.2)
Median [Min, Max]	86.3 [31.9, 288]	96.8 [71.2, 115]	87.5 [31.9, 288]
Missing	14 (8.0%)	0 (0%)	14 (7.4%)
Serum creatinine (mg/dL)			
Mean (SD)	0.863 (0.289)	1.01 (0.159)	0.874 (0.284)
Median [Min, Max]	0.801 [0.360, 2.00]	1.05 [0.710, 1.22]	0.826 [0.360, 2.00]
Bilirubin (mg/dL)			
Mean (SD)	0.649 (0.424)	0.407 (0.138)	0.631 (0.414)
Median [Min, Max]	0.500 [0.160, 2.90]	0.400 [0.200, 0.700]	0.500 [0.160, 2.90]
Albumin (g/L)			
Mean (SD)	36.6 (5.37)	45.6 (3.32)	37.3 (5.74)
Median [Min, Max]	37.0 [24.0, 46.0]	45.5 [38.0, 50.0]	38.0 [24.0, 50.0]
Missing	1 (0.6%)	0 (0%)	1 (0.5%)
ALP (U/L)			
Mean (SD)	135 (115)	71.4 (18.6)	130 (112)
Median [Min, Max]	99.0 [26.0, 748]	64.5 [47.0, 113]	95.0 [26.0, 748]
ALT (U/L)			
Mean (SD)	29.4 (21.1)	16.3 (5.18)	28.5 (20.6)
Median [Min, Max]	24.5 [4.00, 152]	16.0 [8.00, 31.0]	23.0 [4.00, 152]
AST (U/L)			
Mean (SD)	26.8 (12.7)	18.7 (3.65)	26.2 (12.4)
Median [Min, Max]	24.0 [8.00, 69.0]	18.5 [13.0, 26.0]	23.0 [8.00, 69.0]
Healthy volunteers			
No	174 (100%)	0 (0%)	174 (92.6%)
Yes	0 (0%)	14 (100%)	14 (7.4%)
Sex			
Female	93 (53.4%)	3 (21.4%)	96 (51.1%)
Male	81 (46.6%)	11 (78.6%)	92 (48.9%)
Race			
White	134 (77.0%)	7 (50.0%)	141 (75.0%)
Asian	5 (2.9%)	1 (7.1%)	6 (3.2%)
Black or African American	4 (2.3%)	6 (42.9%)	10 (5.3%)
Missing	27 (15.5%)	0 (0%)	27 (14.4%)
Other	4 (2.3%)	0 (0%)	4 (2.1%)
Ethnicity			
Hispanic or Latino	6 (3.4%)	3 (21.4%)	9 (4.8%)
Not Hispanic or Latino	135 (77.6%)	11 (78.6%)	146 (77.7%)

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Covariates	KO-MEN-001 (N=174)	KO-MEN-003 (N=14)	Total (N=188)
Missing/Not Reported/Unknown	33 (19.0%)	0 (0%)	33 (17.6%)
Age Categories*			
18-39 years old	20 (11.5%)	9 (64.3%)	29 (15.4%)
40-64 years old	60 (34.5%)	5 (35.7%)	65 (34.6%)
≥65 years old	94 (54.0%)	0 (0%)	94 (50.0%)
Body Weight Categories*			
≤60 kg	41 (23.6%)	0 (0%)	41 (21.8%)
61 - ≤75 kg	60 (34.5%)	7 (50.0%)	67 (35.6%)
>75 kg	73 (42.0%)	7 (50.0%)	80 (42.6%)
Baseline Renal Impairment based on eGFR			
Normal	73 (42.0%)	8 (57.1%)	81 (43.1%)
Mild	66 (37.9%)	6 (42.9%)	72 (38.3%)
Moderate	21 (12.1%)	0 (0%)	21 (11.2%)
Missing	14 (8.0%)	0 (0%)	14 (7.4%)
Hepatic Impairment Category			
Normal	137 (78.7%)	14 (100%)	151 (80.3%)
Mild	32 (18.4%)	0 (0%)	32 (17.0%)
Moderate	5 (2.9%)	0 (0%)	5 (2.7%)
ECOG			
Fully active (ECOG=0)	43 (24.7%)	0 (0%)	43 (22.9%)
Restricted in strenuous physical activity (ECOG=1)	98 (56.3%)	0 (0%)	98 (52.1%)
Able to self-care, unable to work (ECOG=2)	33 (19.0%)	0 (0%)	33 (17.6%)
Not evaluated	0 (0%)	14 (100%)	14 (7.4%)

Source: KO-PK-0001, Table 1 and Table 2

Applicant Table 25: Applicant - Parameter Estimates from Final Population PK Model

Parameters	Estimates	IIV(%)	%RSE	95% CI	Shrinkage (%)
F1	0.129 Fixed	IOV: 1.06			Occ 1: 2.86 Occ 2: 31.8

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					Occ 3: 36.0
Effect of PPI on F1	× 0.627		11.5%	0.500 - 0.784	
Effect of FED on F1	× 6.09		12.2%	4.22 – 7.11	
Ka (1/h)	0.0928		20.2%	0.0624 – 0.138	-
Effect of PPI on Ka	× 0.616		13.3%	0.474 – 0.799	
Lag time (h)	0.325	-	4.44%	0.297 – 0.354	-
Effect of FED on Lag	× 1.38		20.4%	0.925 – 2.06	
CL (L/h)	11.6	47.3%	11.7%	9.23 – 14.6	39.3%
Healthy volunteers on CL	×2.59		15.0%	1.93 – 3.47	
Strong CYP3A4 inhibitors on CL	×0.459		11.3%	0.368 – 0.573	
Vc (L)	54.6	120%	25.4%	33.2 – 89.9	22.2%
Q (L/h)	27.7	-	25.3%	16.9 – 45.4	-
Vp (L)	1106	-	6.38%	976 – 1253	-
Residual Error	Estimates				
Proportional (%)	43.7		2.71%	41.3 – 46.0	

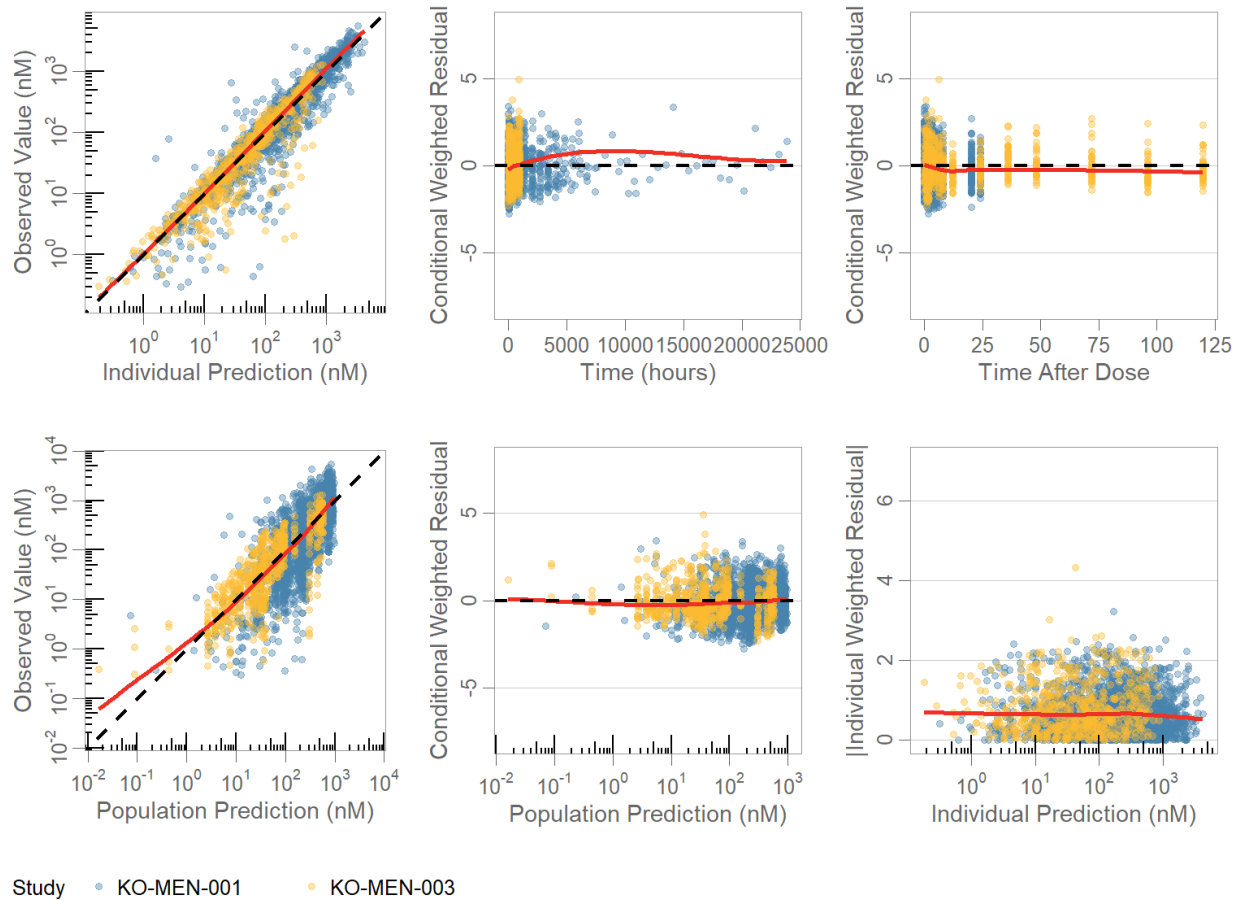
Source: KO-PK-0001, Table 9

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Applicant Figure 4: Applicant - Goodness-of-fit Plots for the Final Population PK Model



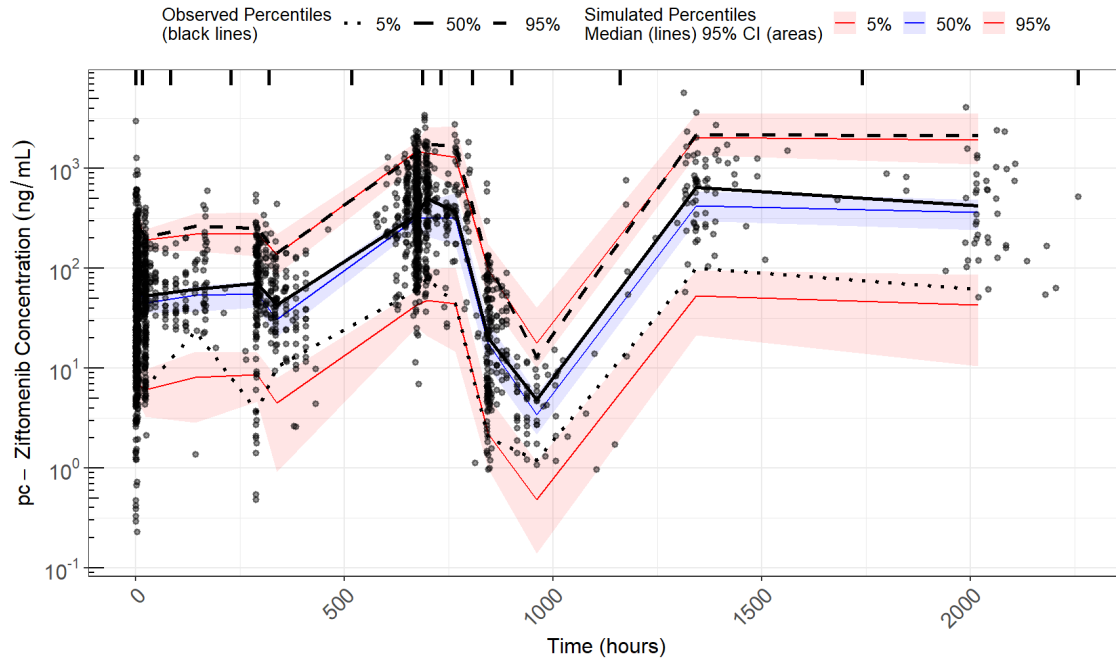
Source: KO-PK-0001, Figure 159

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Applicant Figure 5: Applicant - VPC of Final Population PK Model



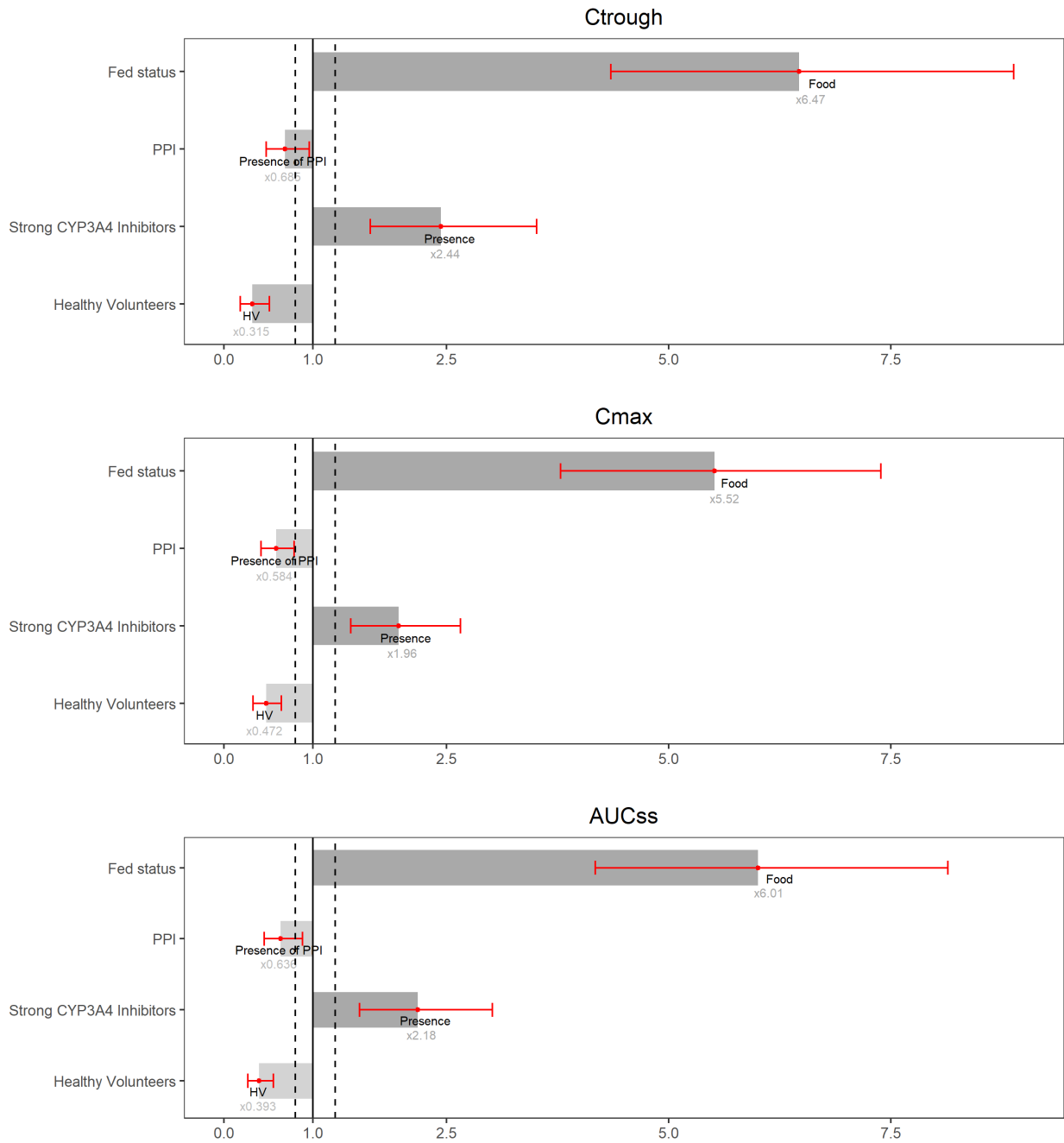
Source: KO-PK-0001, Figure 16

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Applicant Figure 6: Applicant - Impact of Significant Covariates on Exposure



Reference subject: Patient without PPI, without strong CYP3A4 inhibitor, and without food

Source: KO-PK-0001, Figure 12

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The FDA's Assessment:

The PopPK model is adequate to describe the observed PK data of ziftomenib in adult patients with R/R AML. There is no clinical meaningful impact for covariates including body weight, sex, race, ethnicity, age (18-86 years old), AML mutation (*NPM1*-m, *KMT2A*-r or others), ALP, ALT, AST, renal and hepatic impairment (mild or moderate), and p-gp inhibition. These covariates were evaluated using forward addition & backward elimination and dropped out from PopPK model. The impact of severe renal or hepatic impairment were not evaluated due to lack of data. Based on the model, typical value of CL an in subjects with co-administration of strong CYP3A4 inhibitors were 54.1% lower than those in subjects without co-administration of CYP3A4 inhibitors. Coadministration of PPI reduced the relative bioavailability (F1) and the first rate of absorption (Ka); F1 and Ka of ziftomenib with PPI would be 37.3% and 38.4% lower than F1 and Ka without PPI, respectively. Administration of ziftomenib in presence of food increased F1 and delayed the absorption; F1 of ziftomenib with food would be ~6.1 times higher than F1 under fasting and the lag time of absorption would be ~1.38 time longer than under fasting condition.

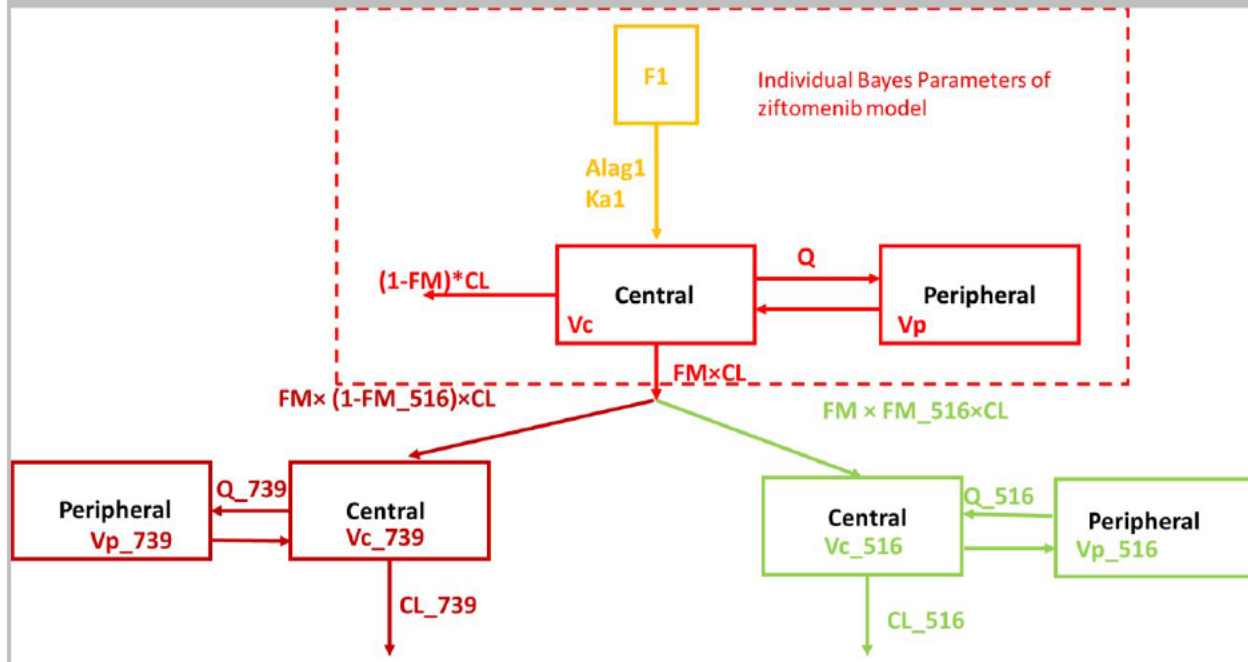
For metabolites KO-516 and KO-739, the PopPK model was developed by sequential 2-stage approach by using empirical Bayesian estimates derived from the final Ziftomenib PopPK model (FDA Figure 5). A two-compartmental model with linear elimination for both metabolites were retained for popPK model. The final popPK model estimates for metabolites are listed as below (FDA Table 60). The GOF plots are listed in FDA Figure 6. The pcVPC plots are listed in FDA Figure 7. The PopPK model is adequate to describe the observed PK data of Ziftomenib metabolites KO-516 and KO-739 in adult patients with R/R AML.

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FDA Figure 5. PopPK Model Structure of Metabolites KO-516 and KO-739



CL = clearance of ziftomenib; CL_{516} = clearance of KO-516; CL_{739} = clearance of KO-739; FM = fraction metabolized; FM_{516} = biotransformation fraction of metabolized amount into KO-516; Q_{516} = inter-compartment transfer rate of KO-516; Q_{739} = inter-compartment transfer rate of KO-739; Vc_{516} = central volume of distribution of KO-516; Vc_{739} = central volume of distribution of KO-739; Vp_{516} = peripheral volume of distribution of KO-516; Vp_{739} = peripheral volume of distribution of KO-739

Source: KO-PK-0001, Feb-27-2025, Figure 20

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FDA Table 60. Final PopPK Parameters of Metabolites

Parameters	Estimates	IIV (%)	%RSE	95% CI	Shrinkage (%)
FM	0.535 Fixed	56.8%			28.1%
Healthy volunteers on FM	×0.348		25.1%	0.207 – 0.551	
FM_516	0.5 Fixed				
CL_739 (L/h)	8.50	74.7%	7.29	7.37 – 9.81	14.8%
Strong CYP3A4 inhibitors on CL_739	×0.195		4.28	0.179 – 0.212	
Q_739 (L/h)	4.13	162%	13.4	3.17 – 5.37	19.8%
Vc_739 (L)	8.20	110%	13.1	6.34 – 10.6	22.5%
Healthy volunteers on Vc_739	×0.197		52.2	0.0709 – 0.549	
Vp_739 (L)	240		6.28	212 – 272	
CL_516 (L/h)	21.7	31.2%	4.671	19.8 – 23.8	29.0%
Strong CYP3A4 inhibitors on CL_516	×0.449		4.84	0.408 – 0.493	
Q_516 (L/h)	9.55	118%	9.97	7.85 – 11.6	26.2%
Vc_516 (L)	11.8	191%	20.6	7.88 – 17.6	22.1%
Healthy volunteers on Vc_516	×0.154		71.4	0.0379 – 0.624	
Vp_516 (L)	604		9.62	500 – 729	
Residual Error	Estimates				
Proportional KO-739 (%)	45.2		2.23	43.2 – 47.2	
Additive KO-739 (ng/mL)	0.128		30.0	0.0527 – 0.203	
Proportional KO-516 (%)	36.4		2.10	34.9 – 37.9	

CI=confidence interval; CL_516= clearance of KO-516; CL_739= clearance of KO-739; CYP3A4= cytochrome P450 3A4; FM = fraction metabolized; FM_516= biotransformation fraction of metabolized amount into KO-516; IIV= inter-individual variability; PK= pharmacokinetic; Q_516= inter-compartment transfer rate for KO-516; Q_739= inter-compartment transfer rate for KO-739; RSE= relative standard error; Vc_516= central volume of distribution of KO-516; Vc_739= central volume of distribution of KO-739; Vp_516= peripheral volume of distribution of KO-516; Vp_739= peripheral volume of distribution of KO-739

Note 1: RSE was derived in NONMEM.

Note 2: The IIV is presented as the % coefficient of variation of the random effect ($100 \times (\exp(\omega^2)-1)0.5$).

Note 3: Condition number is 30.78

Source: KO-PK-0001, Feb-27-2025, Table 13

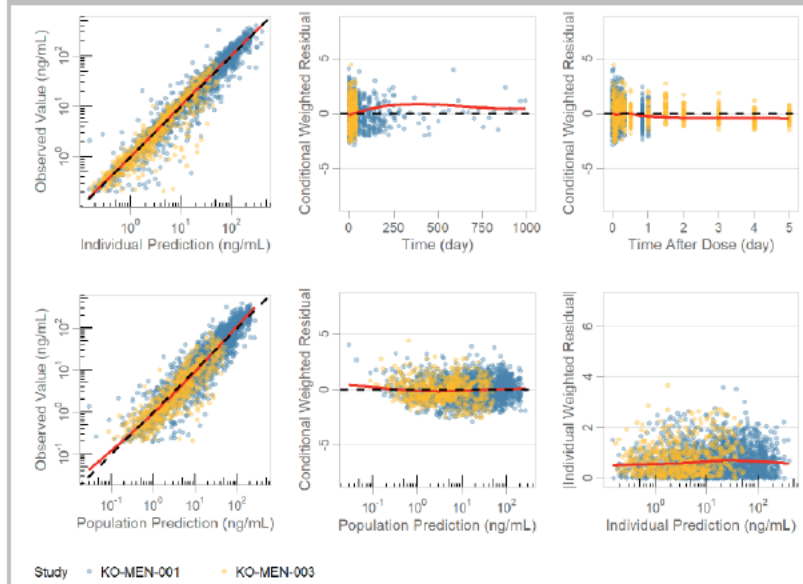
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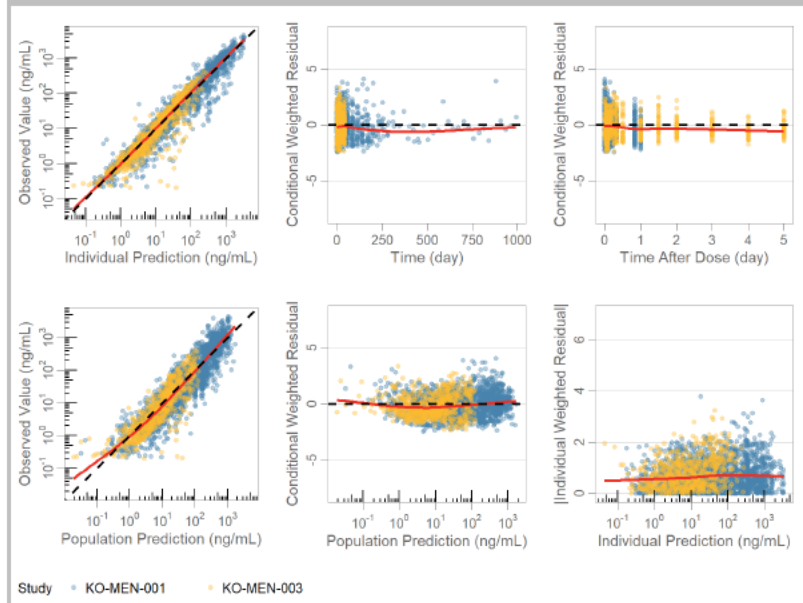
Komzifti (ziftomenib)

FDA Figure 6. GOF Plots for Ziftomenib metabolites, KO-516 (a) and KO-739 (b)

a. KO-516



b. KO-739



LOESS= locally weighted scatter plot smoothing; PK= pharmacokinetic

Note: Red lines represent LOESS lines

Source: KO-PK-0001, Figure 21 and 22

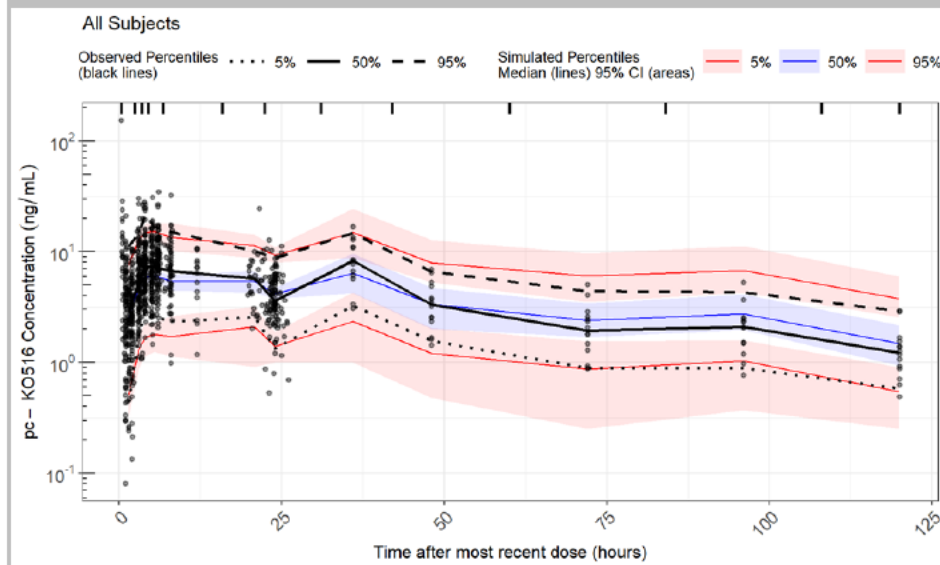
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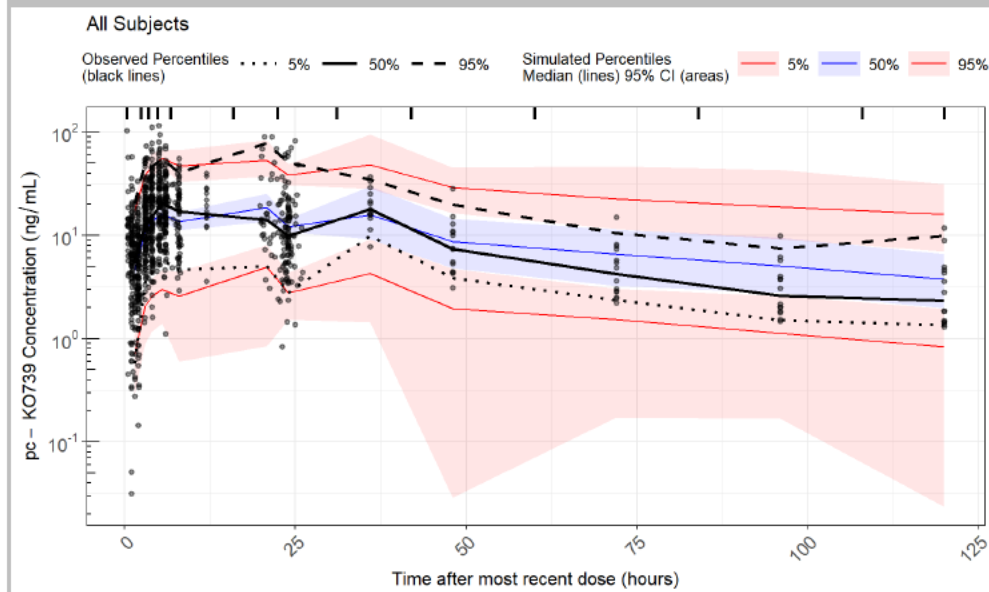
Komzifti (ziftomenib)

FDA Figure 7. Final pcVPC plots for KO-516 (a) and KO-739 (b)

a. KO-516



b. KO-739



Notes: Black dots are observed data points; black solid line is the observed median; black dashed lines are observed 5th and 95th percentiles. The blue area is the 95% CI of the simulated median, and pink areas are the 95% CI of the simulated 5th and 95th percentiles. CI= confidence interval; pc= prediction-corrected; PK= pharmacokinetic

Source: KO-PK-0001, Figure 23 and 24

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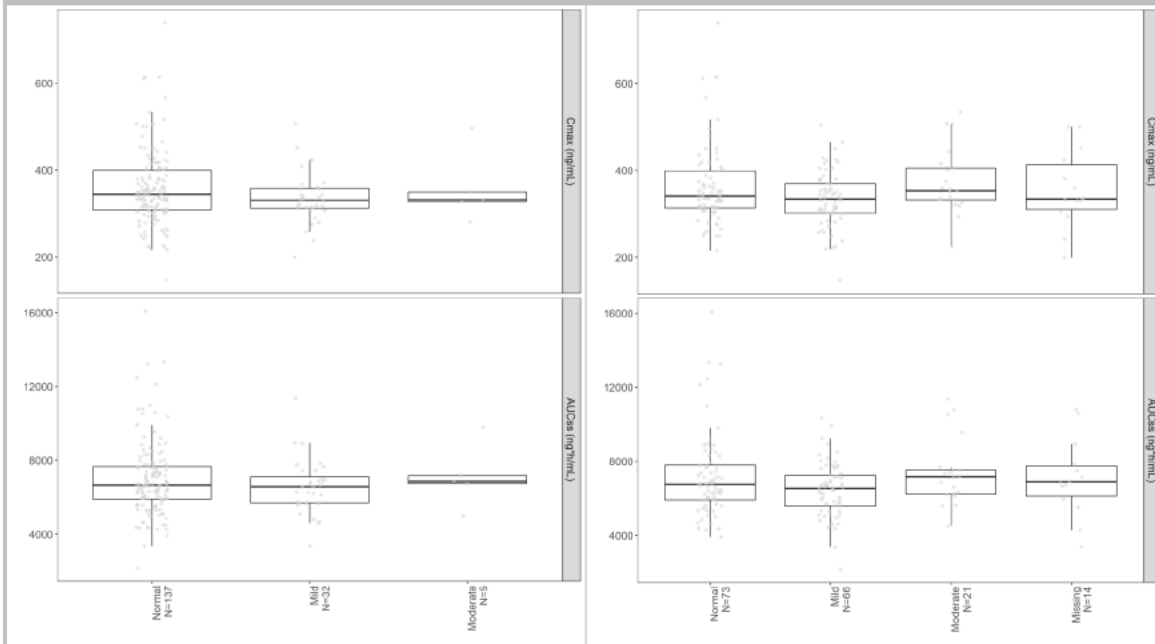
14.4.2.3. PPK Review Issues

Based on popPK, mild or moderate hepatic and renal impairment have no clinical meaningful impact on Ziftomenib exposure (FDA Figure 8).

FDA Figure 8. Distribution of Ziftomenib Exposure by Hepatic (a) and Renal (b) Impairment Group in Study KO-MEN-001

a. Hepatic Impairment

b. Renal Impairment



AUCss= area under the concentration-time curve at steady state dosing interval;
Cmax=maximum concentration at steady state; *N*= number of subjects

Source: KO-PK-0001, Figure 13 and 14

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14.4.2.4. Reviewer's Independent Analysis

A high percentage of study subjects received concomitant medications and is summarized as below (FDA Table 61).

FDA Table 61. Summary of Concomitant Medications

Covariate Category	N (%)		
	KO-MEN-001 (N=174)	KO-MEN-003 (N=14)	Overall (N=188)
PPI			
Absence	109 (62.6%)	0 (0%)	109 (58.0%)
Presence	65 (37.4%)	14 (100%)	79 (42.0%)
H2 Blocker			
Absence	94 (54.0%)	14 (100%)	108 (57.4%)
Presence	80 (46.0%)	0 (0%)	80 (42.6%)
P-gp Inhibitor			
Absence	54 (31.0%)	14 (100%)	68 (36.2%)
Presence	120 (69.0%)	0 (0%)	120 (63.8%)
Cytochrome P-450 3A4 Inhibitors			
Absence	19 (10.9%)	14 (100%)	33 (17.6%)
Presence (weak)	13 (7.5%)	0 (0%)	13 (6.9%)
Presence (moderate)	12 (6.9%)	0 (0%)	12 (6.4%)
Presence (strong)	130 (74.7%)	0 (0%)	130 (69.1%)
Cytochrome P-450 3A4 Inducers			
Absence	90 (51.7%)	14 (100%)	104 (55.3%)
Presence (weak)	84 (48.3%)	0 (0%)	84 (44.7%)

N= number of subjects; *H2* = histamine H2 receptor; *P-gp*= *p-glycoprotein*; *PPI*= *proton pump inhibitor*
Note: Subjects with presence of concomitant medication had at least one PK samples flagged with concomitant medication.

Source: KO-PK-0001, Table 4

The review team analyzed the impact of Cyp3A4 inhibitor and proton-pump inhibitor (PPI) on steady state ziftomenib exposure distribution based on simulation using post-hoc parameter derived in the PopPK model (FDA Figure 9). The result is consistent with the applicant analysis in Applicant Figure 6. Only strong Cyp3A inhibitor but not weak and moderate type can cause 2-3 fold increase in ziftomenib exposure parameters. The presence of PPI can slightly decrease Ziftomenib exposures. These exposure changes are not likely clinically significant based on flat ER efficacy relationship.

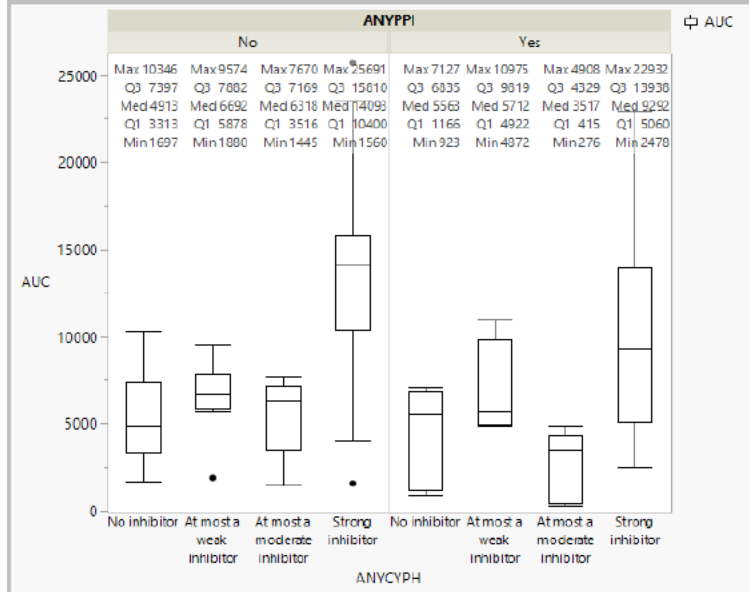
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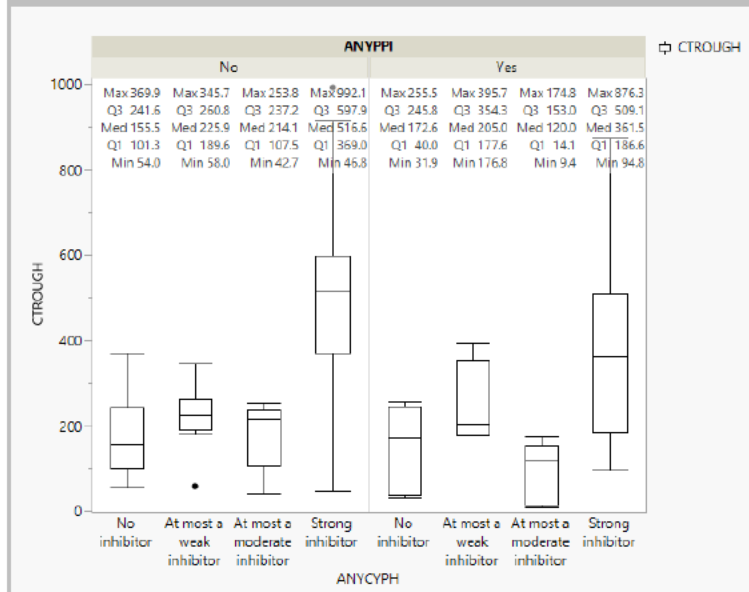
Komzifti (ziftomenib)

FDA Figure 9. Distribution of Ziftomenib Exposure by Cyp3A inhibitor and PPI by AUC (a), Ctrough (b), and Cmax (c)

a. AUC



b. Ctrough



Version date: March 1, 2024 (ALL NDA/ BLA reviews)

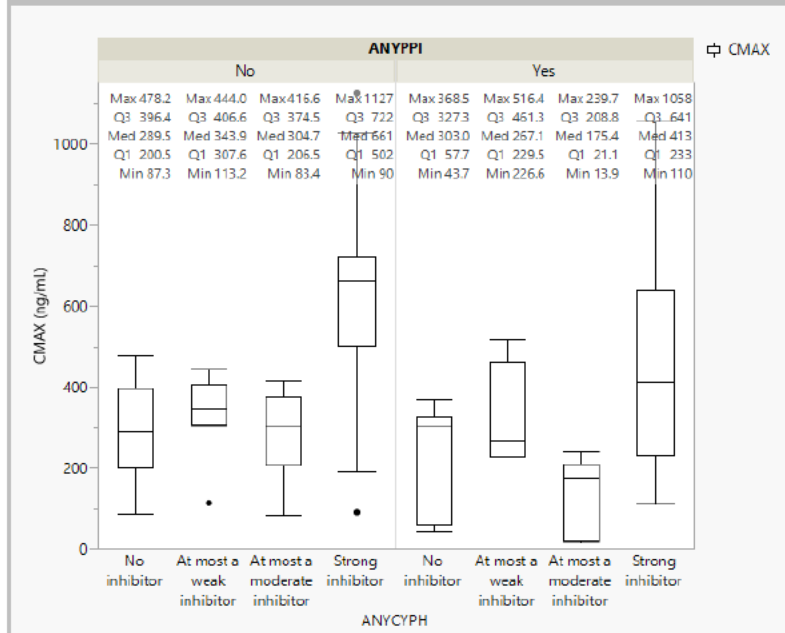
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c. Cmax



AUC unit: $ng \cdot h/mL$, Cmax and Ctrough unit: ng/mL

Source: Reviewer's analysis

14.4.3. Exposure-Response Analysis

14.4.3.1. ER (efficacy) Executive Summary

The FDA's Assessment:

The Applicant conducted ER efficacy analysis using data from 100 patients with *NPM1*-m R/R AML. The Applicant used combination of efficacy endpoints including:

1. Overall response (PR, MLFS, CRp, CRi, CRh, CR, CRmrd-),
2. Overall response (SD, CB, MLFS, PR, CRp, CRi, CRh, CR, CRmrd-),
3. Overall response (MLFS, CRp, CRi, CRh, CR, CRmrd-),
4. Complete/partial response (CR, CRmrd- or CRh),
5. Complete/partial response (CRp, CRi, CRh, CR, CRmrd-),
6. Complete/partial response (CR, CRmrd-).

Among these combination endpoints, complete/partial response (CR, CRmrd- or CRh) and complete/partial response (CR, CRmrd-) are considered most relevant for regulatory purposes after consultation with clinical reviewer. Based on the analysis results, the

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relationship between ziftomenib and its efficacy endpoints are mainly flat. Overall, the applicant's ER analysis is considered acceptable for the purpose of characterizing the ER relationship of ziftomenib and its efficacy endpoints.

14.4.3.2. ER (efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis	To assess the ER relationships between ziftomenib exposure and the efficacy endpoints in patients with R/R AML	
Study Included	Study KO-MEN-001	
Endpoint	Primary: CR/CRh rate Secondary: Duration of CR/CRh, TI, CR/CRh MRD negativity, CRc, EFS, OS	
No. of Patients (total, and with individual PK)	Total 139 (NPM1-m 100)	
Population Characteristics (Applicant Table 26)	General	<u>Age</u> : median 66 years (range 21-86 years) <u>Weight</u> : median: 71.4 kg (range: 41-135 kg) <u>Sex</u> : 61 (43.9%) male, 78 (56.1%) female <u>Race</u> : White, 107 (77%); Asian, 4 (2.9%); Black or African American, 3 (2.2); Missing, 22 (15.8); Other, 3 (2.2%)
	Pediatrics (if any)	None.
Dose(s) Included	200 mg and 600 mg QD	
Exposure Metrics Explored (range)	Steady state AUC, C _{max} and C _{trough}	
Covariates Evaluated	Age, sex, race, ethnicity, weight, height, BMI, BSA, markers of renal and hepatic functions, AML mutations, Eastern Cooperative Oncology Group performance status [ECOG], presence of P-gp inhibitors, presence of PPI and presence of CYP3A inducers or inhibitors	
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Various logistic regression models were constructed to assess the statistical relationships between exposure, potential risk factors and the probability	Adequate

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	of responses based on the above six combinations of efficacy endpoints. Logistic regression models were constructed to assess the effects of ziftomenib. The best fitting model according to Akaike information criterion (AIC) was selected.	
Model Parameter Estimates	Applicant Table 27	Adequate
Model Evaluation	AIC	Adequate
Covariates and Clinical Relevance	No covariates of clinical relevance were identified.	Adequate
Simulation for Specific Population	None	N/A
Visualization of E-R relationships	Applicant Figure 7 presents primary efficacy endpoint. Refer to KO-PK-0001, Figures 25, 26, and 28 for other efficacy endpoints assessed.	Adequate
Overall Clinical Relevance for ER	In <i>NPM1</i> -m R/R AML patients, none of the exposure parameters of ziftomenib were statistically (i.e. p-value > 0.05) related to any probability of efficacy endpoints.	Adequate
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	There is no efficacy ER description in USPI section 12.2.	N/A

Applicant Table 26: Applicant - Summary of Baseline Characteristics and Laboratory Values in the Dataset

Covariates	<i>NPM1</i> -m (N=100)	<i>KMT2A</i> -r (N=25)	Total (N=139)
Age (years)			
Mean (SD)	65.2 (13.0)	48.6 (17.4)	62.3 (15.1)
Median [Min, Max]	69.0 [22.0, 86.0]	49.0 [21.0, 80.0]	66.0 [21.0, 86.0]
Weight (kg)			
Mean (SD)	73.6 (17.9)	76.7 (15.8)	74.8 (18.3)
Median [Min, Max]	71.1 [41.0, 126]	72.1 [51.0, 118]	71.4 [41.0, 135]
Height (cm)			
Mean (SD)	167 (9.44)	169 (10.2)	168 (9.61)

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Median [Min, Max]	166 [149, 188]	167 [154, 188]	167 [149, 188]
BMI (kg/m²)			
Mean (SD)	26.2 (5.91)	26.8 (5.19)	26.4 (6.08)
Median [Min, Max]	25.6 [14.2, 47.5]	25.5 [17.1, 39.9]	25.4 [14.2, 52.7]
BSA (m²)			
Mean (SD)	1.82 (0.229)	1.86 (0.212)	1.83 (0.232)
Median [Min, Max]	1.82 [1.37, 2.33]	1.80 [1.57, 2.43]	1.81 [1.37, 2.46]
eGFR (mL/min/1.73m²)			
Mean (SD)	89.9 (28.0)	104 (54.1)	91.3 (33.7)
Median [Min, Max]	85.0 [31.9, 172]	95.1 [34.8, 288]	83.9 [31.9, 288]
Serum creatinine (mg/dL)			
Mean (SD)	0.831 (0.271)	0.872 (0.326)	0.856 (0.284)
Median [Min, Max]	0.785 [0.360, 1.86]	0.820 [0.390, 2.00]	0.803 [0.360, 2.00]
CrCL (mL/min)			
Mean (SD)	89.1 (33.0)	119 (59.7)	93.5 (40.3)
Median [Min, Max]	84.7 [30.9, 211]	105 [37.0, 306]	85.5 [30.9, 306]
Bilirubin (mg/dL)			
Mean (SD)	0.610 (0.382)	0.623 (0.440)	0.628 (0.398)
Median [Min, Max]	0.500 [0.160, 2.20]	0.500 [0.200, 2.30]	0.500 [0.160, 2.30]
Albumin (g/L)			
Mean (SD)	37.3 (5.21)	37.2 (5.55)	37.3 (5.14)
Median [Min, Max]	37.6 [24.0, 46.0]	38.0 [25.0, 45.0]	38.0 [24.0, 46.0]
ALP (U/L)			
Mean (SD)	122 (75.9)	106 (56.5)	119 (72.6)
Median [Min, Max]	94.5 [26.0, 427]	98.0 [41.0, 276]	95.0 [26.0, 427]
ALT (U/L)			
Mean (SD)	26.5 (18.4)	32.8 (19.8)	28.5 (19.0)
Median [Min, Max]	23.5 [4.00, 119]	28.0 [10.0, 92.0]	24.0 [4.00, 119]
AST (U/L)			
Mean (SD)	25.1 (10.9)	24.9 (10.2)	25.4 (10.8)
Median [Min, Max]	23.0 [10.0, 59.0]	24.0 [11.0, 57.0]	23.0 [9.00, 59.0]
Sex			
Male	39 (39.0%)	13 (52.0%)	61 (43.9%)
Female	61 (61.0%)	12 (48.0%)	78 (56.1%)
Race			
White	78 (78.0%)	21 (84.0%)	107 (77.0%)
Asian	3 (3.0%)	1 (4.0%)	4 (2.9%)
Black or African American	2 (2.0%)	1 (4.0%)	3 (2.2%)
Missing	15 (15.0%)	2 (8.0%)	22 (15.8%)
Other	2 (2.0%)	0 (0.0%)	3 (2.2%)
Ethnicity			

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Hispanic or Latino	78 (78.0%)	22 (88.0%)	109 (78.4%)
Not Hispanic or Latino	1 (1.0%)	2 (8.0%)	3 (2.2%)
Missing/Not Reported/Unknown	21 (21.0%)	1 (4.0%)	27 (19.4%)
Baseline Renal Impairment based on eGFR			
Normal	44 (44.0%)	12 (48.0%)	59 (42.4%)
Mild	38 (38.0%)	7 (28.0%)	54 (38.8%)
Moderate	11 (11.0%)	4 (16.0%)	16 (11.5%)
Missing	7 (7.0%)	2 (8.0%)	10 (7.2%)
ECOG			
Fully active (ECOG=0)	28 (28.0%)	7 (28.0%)	37 (26.6%)
Restricted in strenuous physical activity (ECOG=1)	58 (58.0%)	15 (60.0%)	82 (59.0%)
Able to self-care, unable to work (ECOG=2)	14 (14.0%)	3 (12.0%)	20 (14.4%)
AML Mutation			
<i>NPM1</i> -m alone	100 (100%)	0 (0.0%)	100 (71.9%)
<i>KMT2A</i> -r alone	0 (0.0%)	25 (100%)	25 (18.0%)
<i>Other Mutation</i>	0 (0.0%)	0 (0.0%)	14 (10.1%)

Source: KO-PK-0001, Table 14 and Table 15

Applicant Table 27: Applicant - Parameter Estimates from Final ER Model of Efficacy Endpoint

Efficacy Endpoints	<i>NPM1</i> -m Mutation (N=100)		<i>KMT2A</i> -r Mutation (N=25)		Overall Population (N=139)	
	N Responders	% (95% CI)	N Responders	% (95% CI)	N Responders	% (95% CI)
OR: MLFS, CRp, CRi, CRh, CR, CRmrd-	40	40.0% (30.5, 50.3)	3	12.0% (3.15, 32.3)	44	31.7% (24.2, 40.2)
Complete/Partial Response: CR, CRmrd- or CRh	28	28.0% (19.7, 38.0)	2	8.0% (1.40, 27.5)	31	22.3% (15.9, 30.3)
Complete/Partial Response: CRp, CRi, CRh, CR, CRmrd-	33	33.0% (24.1, 43.2)	3	12.0% (3.15, 32.3)	37	26.6% (19.7, 34.9)

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Version date: March 1, 2024 (ALL NDA/ BLA reviews)

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Complete/Partial Response: CR, CRmrd-	21	21.0% (13.8, 30.5)	0	0% (0, 16.6)	22	15.8% (10.4,23.2)

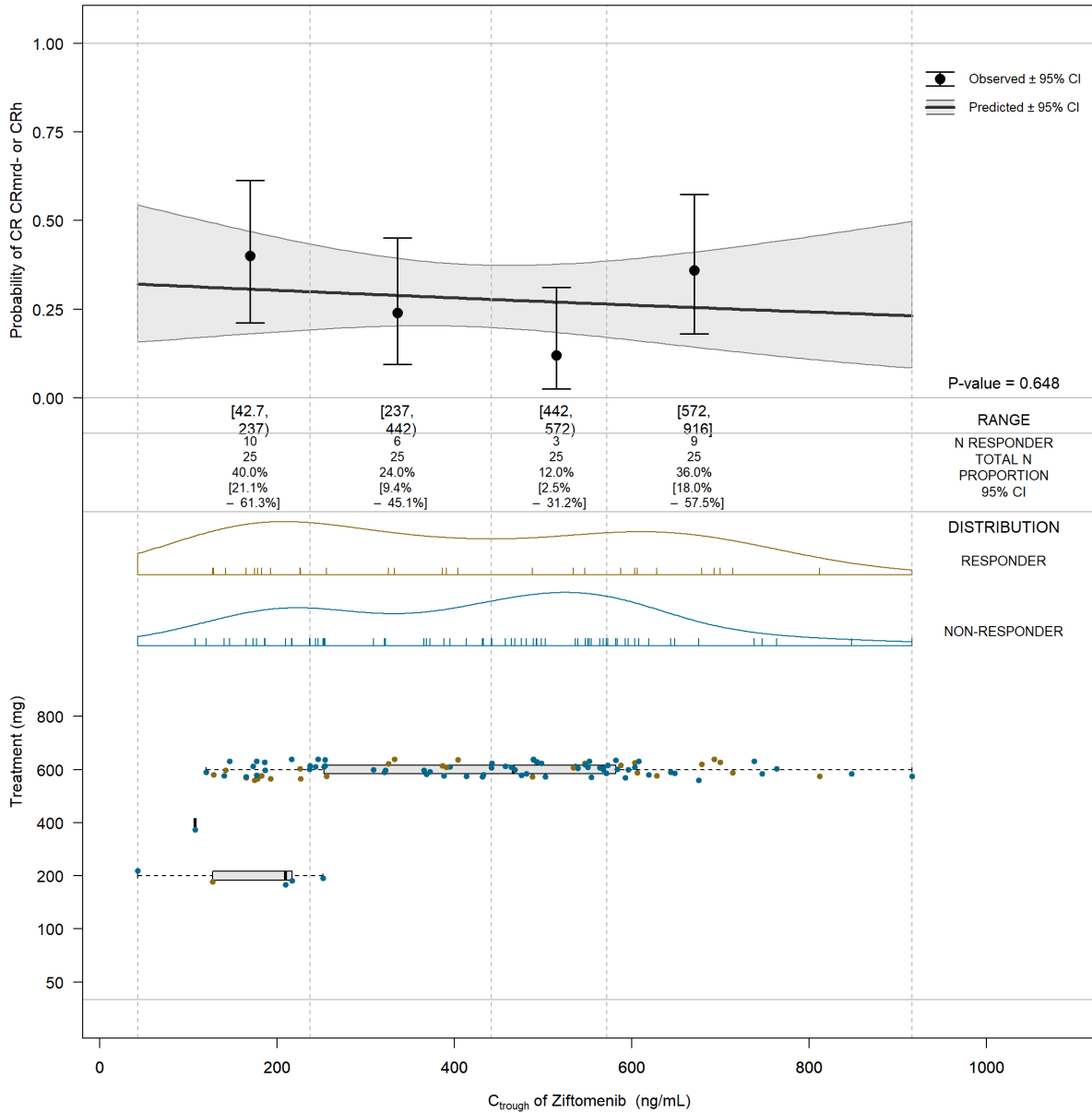
Source: KO-PK-0001, Table 14.1 (Appendix 4)

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Applicant Figure 7: Applicant - ER Curve of Complete/Partial Response (CR, CRmrd- or CRh) vs Ctrough of Ziftomenib for the NPM1-m Efficacy Population



Source: KO-PK-0001, Figure 27

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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14.4.3.3. ER (safety) Executive Summary

The FDA's Assessment:

The Applicant conducted ER safety analysis in all patients with at least one measurable concentration of ziftomenib (N=174). The analysis is conducted on the following endpoints based on the occurrence $\geq 10\%$ criteria: 1) any TEAE grade 3+ AEs, 2) any TEAE grade 4+ AEs, 3) any TRAE grade 3+, 4) any TRAE grade 4+, 5) grade 3+ treatment-emergent anemia, 6) grade 3+ treatment-emergent febrile neutropenia, 7) grade 3+ treatment-emergent neutropenia, 8) grade 3+ treatment-emergent pneumonia, 9) grade 3+ treatment-emergent sepsis, 10) grade 3+ treatment-emergent thrombocytopenia, 11) treatment-emergent differentiation syndrome, and 12) treatment-related differentiation syndrome. There is no positive trend identified between ziftomenib exposure parameters and ER safety endpoints. Overall, the Applicant's ER analysis is considered acceptable for the purpose of assessing the ER relationship of ziftomenib and its safety endpoints.

14.4.3.4. ER (safety) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis	To assess the ER relationships between ziftomenib exposure and the safety endpoints in patients with R/R AML	
Study Included	Study KO-MEN-001	
Population Included	Patients with R/R AML	
Endpoint	Key secondary safety/tolerability - Incidence and severity of AEs according to NCI CTCAE v5.0, Incidence of SAEs, Deaths on treatment, Discontinuations of study treatment due to AEs, Clinically significant changes in clinical laboratory parameters, vital signs parameters, ECG parameters, Change in ECOG status	
No. of Patients (total, and with individual PK)	Total 174 (NPM1-m 119)	
Population Characteristics (Applicant Table 24)	General	<u>Age</u> : median 64.5 years (range: 18-86 years) <u>Weight</u> : median: 71.5 kg (range: 41-135 kg) <u>Sex</u> : 92 (48.9%) male, 96 (51.1%) female <u>Race</u> : White, 141 (75%); Asian, 6 (3.2%); Black or African American, 10 (5.3%); Missing, 27 (14.4%); Other, 4 (2.1%)

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	Organ impairment	Hepatic (NCI-ODWG): Normal, 137 (78.7%); Mild, 32 (18.4%); Moderate, 5 (2.9%) Renal (eGFR): Normal, 73 (42%); Mild, 66 (37.9%); Moderate, 21 (12.1%); Missing, 14 (8%)
	Pediatrics (if any)	None.
	Geriatrics (if any)	Geriatric patients were included in the ER analysis. The age range was 18-86 years.
Dose(s) Included		200 mg and 600 mg QD
Exposure Metrics Explored (range)		Steady state AUC, C _{max} and C _{trough}
Covariates Evaluated		Age, sex, race, ethnicity, weight, height, BMI, BSA, markers of renal and hepatic functions, AML mutations, Eastern Cooperative Oncology Group performance status [ECOG], presence of P-gp inhibitors, presence of PPI and presence of CYP3A inducers or inhibitors.
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Various logistic regression models were constructed to assess the statistical relationships between exposure, potential risk factors and the probability of responses based on the above six combinations of efficacy endpoints. Logistic regression models were constructed to assess the effects of ziftomenib. The best fitting model according to Akaike information criterion (AIC) was selected.	Adequate
Model Parameter Estimates	Applicant Table 28	Adequate
Model Evaluation	AIC	Adequate
Covariates and Clinical Relevance	There were no covariates that had a clinically meaningful impact on treatment-emergent or treatment-related DS. There were no covariates that had a statistically significant relationship with Grade 4+ TEAEs.	Adequate
Simulation for Specific Population	None	N/A
Visualization of E-R relationships	Applicant Figure 8	Adequate

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Overall Clinical Relevance for ER	In <i>NPM1-m</i> R/R AML patients none of the exposure parameters of ziftomenib were statistically (i.e. p-value > 0.05) related to any of the safety endpoints.	Adequate
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	There is no safety ER description in USPI section 12.2.	N/A

Applicant Table 28: Applicant - Parameter Estimates from Final ER Model of Safety (Logistic Regression for Probability of Adverse Events)

Adverse Events	Exposure	AIC	p-value
Any grade 3+ TEAE	Reference (No Exposure)	65.77567	
	C _{max} Ziftomenib	67.77384	0.96586
	C _{trough} Ziftomenib	67.77401	0.96750
	AUC _{ss} Ziftomenib	67.77562	0.99447
Any grade 4+ TEAE	Reference (No Exposure)	160.7893	
	C _{max} Ziftomenib	162.4325	0.55109
	C _{trough} Ziftomenib	162.5638	0.63516
	AUC _{ss} Ziftomenib	162.5132	0.59976
Any grade 3+ TRAE	Reference (No Exposure)	159.8301	
	C _{max} Ziftomenib	161.8301	0.99454
	C _{trough} Ziftomenib	161.8105	0.88870
	AUC _{ss} Ziftomenib	161.8239	0.93707
Any grade 4+ TRAE	Reference (No Exposure)	84.09362	
	C _{max} Ziftomenib	85.59730	0.48412
	C _{trough} Ziftomenib	85.35263	0.39182
	AUC _{ss} Ziftomenib	85.44131	0.42218
Anaemia (TEAE - grade 3+)	Reference (No Exposure)	129.4471	
	C _{max} Ziftomenib	130.4321	0.31595
	C _{trough} Ziftomenib	130.4597	0.32384
	AUC _{ss} Ziftomenib	130.4173	0.31326

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Adverse Events	Exposure	AIC	p-value
Neutropenia (TEAE - grade 3+)	Reference (No Exposure)	118.8438	
	C _{max} Ziftomenib	120.1558	0.40833
	C _{trough} Ziftomenib	120.2142	0.43000
	AUC _{ss} Ziftomenib	120.1875	0.41999
Differentiation syndrome (TEAE - all grades)	Reference (No Exposure)	126.9469	
	C _{max} Ziftomenib	128.9143	0.85671
	C _{trough} Ziftomenib	128.9180	0.86513
	AUC _{ss} Ziftomenib	128.9466	0.98600
Differentiation syndrome (TRAE - all grades)	Reference (No Exposure)	124.3482	
	C _{max} Ziftomenib	126.2440	0.74691
	C _{trough} Ziftomenib	126.3413	0.93400
	AUC _{ss} Ziftomenib	126.3406	0.93054
Febrile neutropenia (TEAE - grade 3+)	Reference (No Exposure)	129.4471	
	C _{max} Ziftomenib	131.4469	0.98835
	C _{trough} Ziftomenib	131.4411	0.93809
	AUC _{ss} Ziftomenib	131.4436	0.95263
Pneumonia (TEAE - grade 3+)	Reference (No Exposure)	124.3482	
	C _{max} Ziftomenib	125.1666	0.27979
	C _{trough} Ziftomenib	125.6351	0.40111
	AUC _{ss} Ziftomenib	125.4724	0.35210
Sepsis (TEAE - grade 3+)	Reference (No Exposure)	95.95438	
	C _{max} Ziftomenib	96.94809	0.31886
	C _{trough} Ziftomenib	96.88578	0.30674
	AUC _{ss} Ziftomenib	96.94384	0.31912
Thrombocytopenia (TEAE - grade 3+)	Reference (No Exposure)	152.5493	
	C _{max} Ziftomenib	154.1644	0.53557
	C _{trough} Ziftomenib	154.2589	0.59062
	AUC _{ss} Ziftomenib	154.2201	0.56681

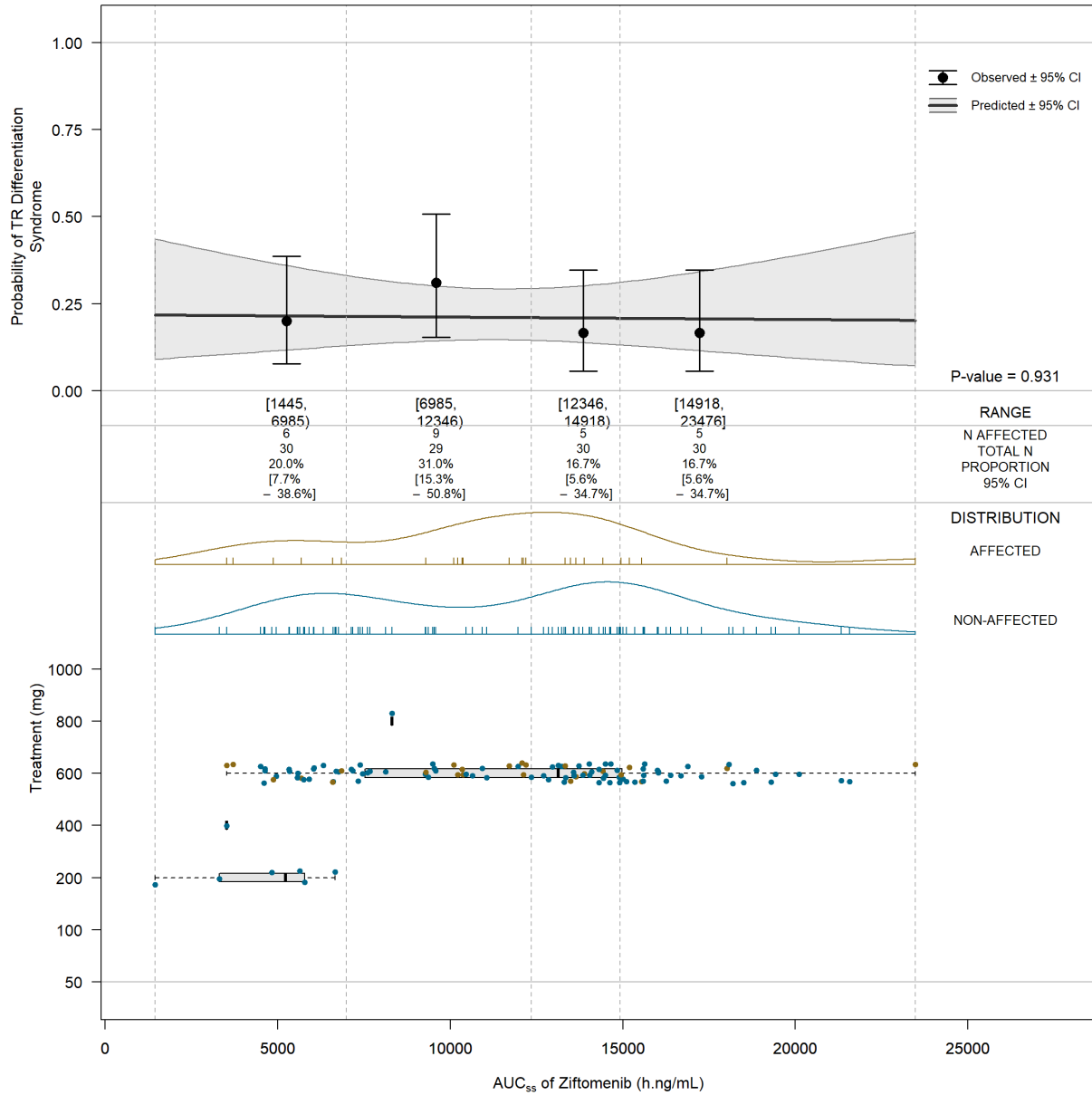
Source: KO-PK-0001, Table 15.4.1 (Appendix 5)

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Applicant Figure 8: Applicant - Probability of TRAE Differentiation Syndrome vs AUCs of Ziftomenib for NPM1-m patients



Source: KO-PK-0001, Figure 34

The FDA's Assessment:

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Acceptable.

14.4.3.5. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The E-R analyses support the overall favorable benefit-risk for ziftomenib. E-R analyses support the proposed dose of 600 mg QD, as it demonstrated robust efficacy in the indicated population, with a manageable safety profile. Ziftomenib is to be administered in fasted state. PPI dosing should be staggered with respect to ziftomenib administration and CYP3A4 inducers are to be avoided. No other covariates were found to have significant or clinically relevant impact on ziftomenib efficacy or safety. Hence no dose adjustment is needed. The proposed ziftomenib dose of 600 mg QD met all requirements for an optimal dose and provides a positive benefit-risk profile.

The FDA's Assessment:

Based on the PopPK and ER analysis result, 600 mg QD dose administered at fasting state is acceptable. No dose adjustment is necessary when co-administered ziftomenib with CYP3A inhibitors. Please refer to the PBPK review for the appropriateness of staggered PPI dosing.

14.4.4. Physiologically based Pharmacokinetic Modeling

14.4.4.1. Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to:

- evaluate the drug-drug interaction (DDI) potential of ziftomenib in patients with cancer
 - as an object of Strong (itraconazole), moderate (fluconazole) and weak (cimetidine) CYP3A inhibitors
 - as an object of strong (rifampin), moderate (efavirenz) and weak (dexamethasone) CYP3A inducers
 - as an inhibitor of CYP3A and UGT1A1
- evaluate the effect of staggered dosing of a proton pump inhibitor (PPI) on ziftomenib exposure.

The Division of Pharmacometrics has reviewed the PBPK submission (reports ko-adme-0201-kurg1g-pbpbk and ko-pk-0004 and related model summary reports, responses to FDA PBPK information requests dated June 20, 2025 (seq0018), July 28, 2025 (seq0026), and July 31, 2025 (seq0024), and the modeling supporting files), to conclude the following:

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Version date: March 1, 2024 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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- The PBPK analyses are inadequate to predict the effects of CYP3A precipitants on ziftomenib exposure in patients with cancer because the available PK data from the patients cannot verify the fraction of ziftomenib metabolized by CYP3A. Therefore, drug interactions of ziftomenib with CYP3A precipitants were estimated based on in vitro phenotyping, human mass balance and absolute bioavailability data:
 - The strong CYP3A inhibitors itraconazole and posaconazole were estimated to increase ziftomenib exposure up to 3-fold.
 - The moderate CYP3A inhibitors isavuconazole, erythromycin, and fluconazole were estimated to increase ziftomenib exposure up to 2-fold.
 - The strong CYP3A inducer rifampin was estimated to reduce ziftomenib exposure by up to 80%.
 - The moderate CYP3A inducer efavirenz was estimated to reduce ziftomenib exposure by up to 70%.
 - The weak CYP3A inducer dexamethasone was estimated to reduce ziftomenib exposure by up to 50%.
 - Low fraction absorbed (approximately 30%) and potentially greater than 30% of the drug was excretion as unchanged parent indicate a potential role of P-gp and BCRP in ziftomenib absorption and excretion.
- Ziftomenib is expected to have a weak-to-moderate inhibitory effect on the sensitive CYP3A substrate midazolam and have minimal effects on the UGT1A1 substrate raltegravir and substrates of CYP2C isoforms.
- The PBPK analyses do not support staggered dosing of PPIs to help minimize the interactions between PPIs and ziftomenib following multiple-dose administration.

14.4.4.2. Background

Ziftomenib (also known as KO-539) is a menin-MLL (KMT2A) inhibitor, which is being developed for the use as monotherapy in the treatment of adult patients with relapsed or refractory acute lymphoblastic leukemia (R/R AML) with a nucleophosmin 1 (*NPM1*) mutation. The proposed dosing regimens of ziftomenib is 600 mg once daily, taken fasted with water at least 1 hour before or 2 hours after a meal. The available dose strength is 200 mg capsule.

Following oral administration of a single dose of 400 mg ziftomenib in healthy subjects under the fasted state, a median time to peak concentration (t_{max}) was approximately 3 hours (KO-MEN-003). Ziftomenib increased more than dose proportionally over the single-dose range of 50 mg to 1000 mg (Cycle 1 Day1 in part 1a) and 200 mg to 800 mg once daily (Cycle 2 Day 1 in phase 1b) in patients with R/R AML (KO-MEN-001). High inter-patient coefficient of variation (CV)% was observed ranging from 89% to 191% in part 1a and from 89% to 243% in part 1b. Steady state was reached within 15 days. Administration of ziftomenib once daily resulted in approximately 5-fold accumulation in AUC₀₋₁₂ at steady state. At the 600 mg dose, the mean steady-state ziftomenib C_{max} was 800 ng/mL and AUC₀₋₂₄ was 12200 ng/mL (KO-PK-0001). Compared to the fasted state, the median t_{max} was delayed 2 hours, AUC and C_{max} increased

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by approximately 4-fold in healthy adults following a single 400 mg ziftomenib dose after a high-fat meal in healthy subjects (KO-MEN-003). Coadministration of a single dose of 20 mg rabeprazole, a gastric acid-reducing agent and proton pump inhibitor (PPI), with a single 400 mg ziftomenib in healthy subjects under the fasted state, ziftomenib AUC_{0-inf} and C_{max} reduced 53% and 70%, respectively (KO-MEN-003). Steady state ziftomenib C_{trough}, C_{max} and AUC were 3.2-, 2.1 and 2.5-fold higher in patients compared to healthy subjects (KO-PK-0001).

Ziftomenib is primarily metabolized by CYP3A4 in vitro (KO-ADME-0050 and KO-ADME-0056). The human ADME study in healthy male adult subjects (KO-MEN-005) following a single oral dose of 400 mg ziftomenib showed that approximately 90.3% of the dose administered orally was recovered, in which approximately 89.7% and 0.53% of the dose were recovered in the feces and the urine, respectively. Ziftomenib accounted for 73.3% of the dose in the feces, whereas 0.028% of the dose was excreted as unchanged drug in the urine, indicating that renal elimination of ziftomenib was minimal. Ziftomenib and its metabolite KO-739 accounted for 15.1% and 9.2% of the total radioactivity exposure in plasma, respectively, and the AUC_{0-inf} of KO-739 was approximately 21% of its parent AUC (KO-MEN-005). Because the metabolite to parent AUC ratio is less than 25%, there is no need to consider the DDI potential of KO-739 (ICH guideline M12). The absolute bioavailability study, conducted along with the human ADME study using an intravenous (IV) microdose of ziftomenib (100 µg), showed that ziftomenib had an oral bioavailability of 12.9%, total plasma clearance of 30.3 L/h, and a renal clearance of 0.0867 L/h (KO-MEN-005). Half-life was 25.1 hour following IV administration of a single 100 mg ziftomenib and 53.5 hours following oral administration of a single 400 mg ziftomenib.

Based on in vitro drug interaction studies, ziftomenib is a time-dependent and reversible inhibitors of CYP3A4 (KO-ADME-0060, -0062 and -0065), and a reversible inhibitor of ziftomenib of UGT1A1, UGT1A9 and UGT2B17 with IC₅₀ values of 3.4, 1.4 and 1.1 µM, respectively (KO-ADME-0061). Ziftomenib increased CYP1A2 mRNA expression in all three donors in a concentration-dependent manner, but not CYP2B6 and CYP3A4 (KO-ADME-0059). Ziftomenib is a substrate of P-gp and BCRP, but not a substrate of MRP2 and BSEP (KO-ADME-0038). Ziftomenib is not an inhibitor of any of the transporters studied (KO-ADME-0038). Refer to the Clinical Pharmacology review section for detail information on ziftomenib regarding ADME properties, in vitro and clinical studies used in the PBPK modeling analyses.

14.4.4.3. Methods

All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Version 23, Certara, Sheffield, UK) unless noted below. Simulations were performed using the default cancer population (Sim-Cancer) model to represent adult patients with cancer and the default healthy subject population model (Sim-Healthy Volunteers) to represent healthy subjects. Schemas of the PBPK modeling and simulation strategy are shown in FDA Figure 10, which summarizes the studies used for model development and verification, and model applications of ziftomenib as an object or precipitant of enzyme induction or inhibition.

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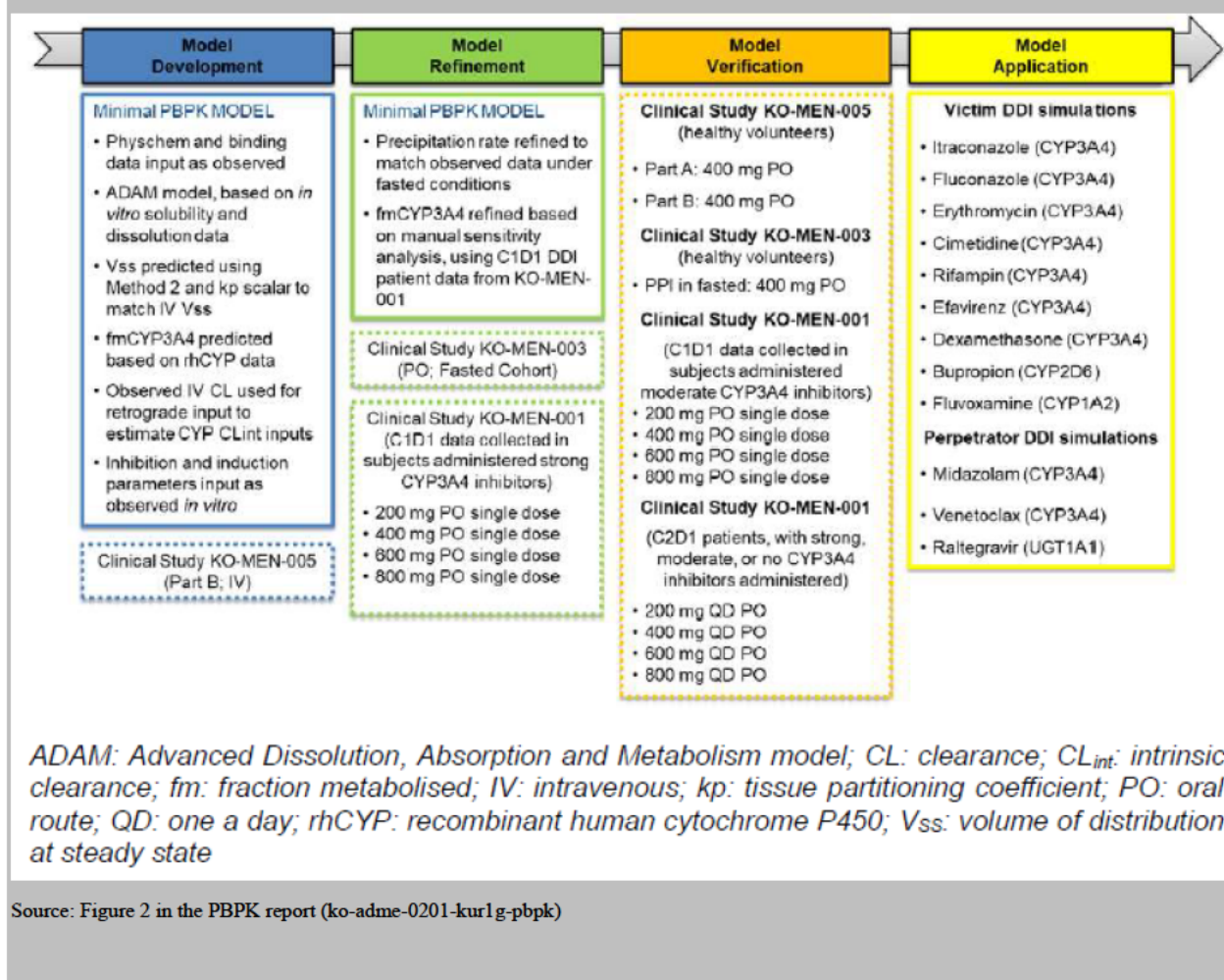
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The ziftomenib PBPK model consists of an Advanced Dissolution, Absorption and Metabolism (ADAM) model for absorption, a full PBPK model for distribution, and an enzyme kinetics model for elimination. The final model input parameters were summarized in FDA Table 62. The values for the inhibition constant (K_i), used in the model, were calculated from *in vitro* IC50 values using the Cheng-Prusoff equation.

The Simcyp library files of the PBPK models for itraconazole (SV-itraconazole_fasted Soln), fluconazole, posaconazole, voriconazole, isavuconazole (RES-isavuconazole), rifampin (SV-Rifampicin-MD), efavirenz, and cimetidine were used without any modification unless otherwise noted. Metabolites of itraconazole (SV-OH-itraconazole) and voriconazole (SV-voriconazole N-oxide) were also considered in the simulations. Additional verification of the ability of the PBPK models of fluconazole, posaconazole and isavuconazole to predict the effects of CYP3A inhibition was presented in NDA218944 PBPK review.

FDA Figure 10. Modeling and simulation strategy



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FDA Table 62. Final input parameters in the PBPK models of ziftomenib

PARAMETER	Value	Source	PARAMETER	Value	Source
<i>Phys Chem and Blood Binding</i>			<i>Distribution – Minimal PBPK</i>		
MW (g/mol)	717.9	Investigator Brochure	K_p scalar	8	Manually optimized to match IV data from Clinical Study KO-MEN-005 Part B
LogP	4.3	Report PSR-KURA-20161215-01-V04	V_{ss} (L/kg)	9.53	Predicted (V23); Method 2
Compound type	Diprotic Base		k_{in} (1/h)	0.3	Manually optimized
pKa 1, 2	9.2, 4.78	Data entry checklist, strongest pKas were selected	k_{out} (1/h)	0.2	
B:P	0.653	Report Ziftomenib_ADMET-0013	V_{loc} (L/kg)	6.8	
f_{up}	0.0002	Report Ziftomenib_ADMET-0014	<i>Interaction</i>		
Main binding protein	HSA	Report KO-ADME-0045	<i>Inhibition</i>		
<i>Absorption - ADAM</i>			CYP3A4 K_i (μ M)	0.903	XT205128 KO539 CYP Inhibition report
$P_{eff,am}$ ($\times 10^{-4}$ cm/s)	3.42	MechPeff prediction; V23 (KUR/1/N report)	CYP2C8 K_i (μ M)	10.3	Calculated via Cheng-Prusoff from IC_{50} value (20.6 μ M) reported in KO-ADME-0065
$P_{max,0}$ (10^{-6} cm/s)	1465.8	MechPeff prediction; V23 (KUR/1/N report)	CYP2C9 K_i (μ M)	4.74	Calculated via Cheng-Prusoff from IC_{50} value (9.48 μ M) reported in KO-ADME-0065
Intrinsic solubility (S_0) (mg/mL)	0.0002	Fitted value from SIVA using data from Preformulation Study Report (KUR/1/N report)	CYP2C19 K_i (μ M)	5.60	Calculated via Cheng-Prusoff from IC_{50} value (11.2 μ M) reported in KO-ADME-0065
Solubility Factor 1 (SF1)	93458	Fitted value from SIVA using data from KO-539 Capsule Dissolution Study (KUR/1/N report)	UGT1A1 K_i (μ M)	1.7415	XT215080 KO539 UGT Inhibition
PRC fasted state (h^{-1})	3.8	Fitted value from SIVA using data from KO-539 Capsule Dissolution Study (KUR/1/N report)	UGT1A9 K_i (μ M)	0.71707	XT215080 KO539 UGT Inhibition
PRC fed state (h^{-1})	0.001	Manually fitted to capture observed food effect	UGT2B17 K_i (μ M)	0.53299	XT215080 KO539 UGT Inhibition
Critical Supersaturation Ratio (CSR)	1.2	Preformulation Study Report	OATP1B1 K_i (μ M)	10.85	Half of IC_{50} ; Report C18033
Capsule kd (min^{-1})	0.035	Fitted value from SIVA using data from KO-539 Capsule Dissolution Study	OATP1B3 K_i (μ M)	4.75	Half of IC_{50} ; Report C18033
SIT Model	Active	Fit for purpose	f_{inac} (0.1 mg/mL in incubation)	0.04	KO-ADME-0046 (applied to CYP2C8, CYP2C9, CYP2C19, UGT1A1, UGT1A9, UGT2B17 K_i) ¹
log K_{mw} neutral	5.472	Predicted, Sincyp V23	f_{inac} (0.3 mg/mL in incubation)	0.011	KO-ADME-0046 (applied to CYP3A4 K_i (0.025 mg/mL used in incubation)) ¹
log K_{mw} ion	3.472	Predicted, Sincyp V23	f_{inac}	1	Assumed (applied to OATP1B1, OATP1B3)
f_{up}	8.45E-05	Predicted, Sincyp V23	CYP3A4 K_i (μ M) - Testosterone	1.2	XT205128 KO539 CYP Inhibition report
<i>Elimination - Enzymatic</i>			CYP3A4 Kinact (1/min) - Testosterone	0.045	
CL_{CV} (L/h)	30.5	Mean of IV data from Clinical Study KO-MEN-005, Part B	CYP3A4 Kinact (1/hr) - Testosterone	2.7	
$f_{ac,CYP1A2}$	0.20	Manually optimized via sensitivity analysis	<i>Induction</i>		
$f_{ac,CYP2D6}$	0.20		CYP1A2 Ind_{max}	3.78	Study XT203128 CYP induction report
$f_{ac,CYP3A4}$	0.60		CYP1A2 $IndC_{50}$ (μ M)	1.71	
CYP1A2 CL_{int} (μ L/min/pmol)	336.7	Retrograde model - healthy volunteers, demographics matched to Clinical Study KO-MEN-005, Part B (KUR/1/N report)	f_{inac}	0.33	Calculated based on Kilford et al. 2008 equation
CYP2D6 CL_{int} (μ L/min/pmol)	1924.2				
CYP3A4 CL_{int} (μ L/min/pmol)	363.5				
f_{inac}	1.00	Assumed, retrograde approach			
CL_{total} (L/h)	0.0857	KO-MEN-005 Part A			

Source: Tables 2B in Response to FDA Clin Pharm IR dated July 28, 2025 (seq0026)

14.4.4.4. Results

14.4.4.4.1. Verification of the PBPK model of ziftomenib

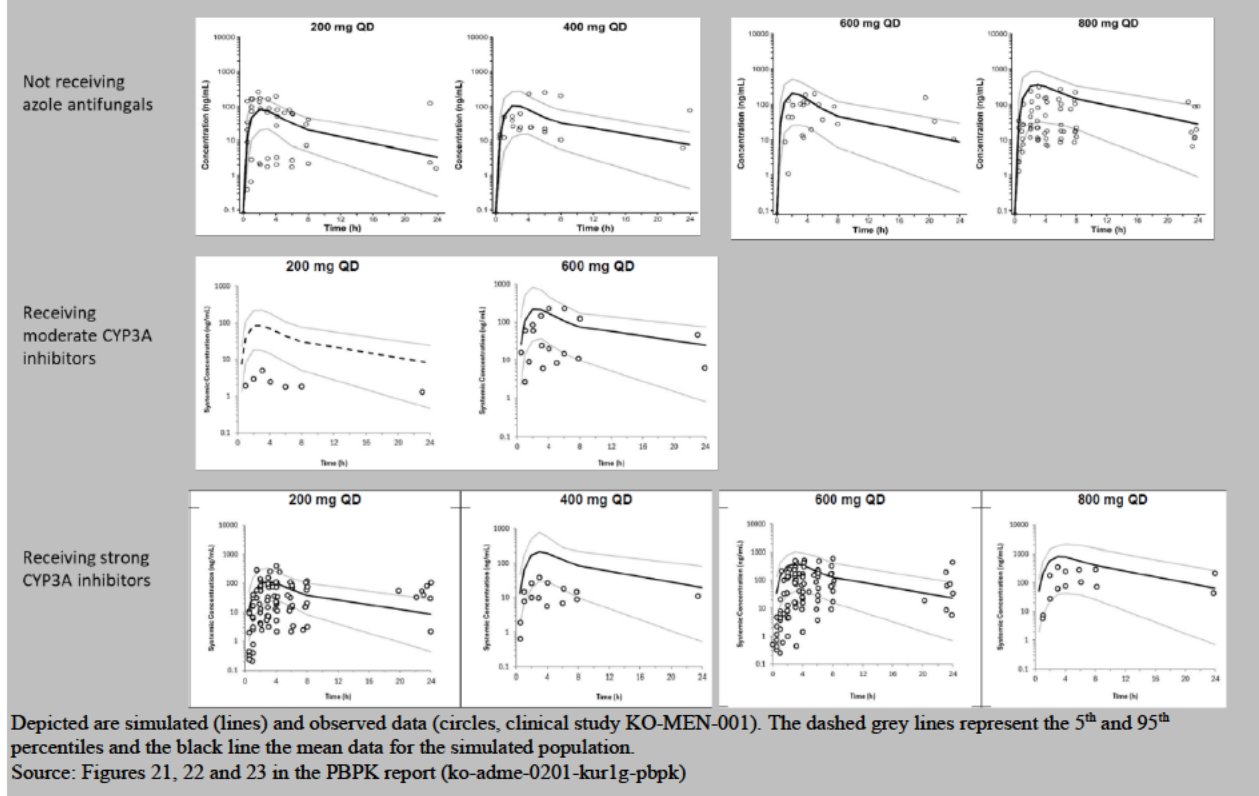
Clinical PK data that had not been used in model development was used to verify the ability of the PBPK models of ziftomenib to describe the PK profiles of ziftomenib. The observed and simulated PK profiles and PK parameters of ziftomenib, following administration of 200, 400, 600 or 800 mg once daily dosing to patients with cancer in the presence or absence of CYP3A inhibitors, were compared and are shown in FDA Figure 11, FDA Figure 12, FDA Table 63, and FDA Table 64. A comparison of simulated and observed ziftomenib exposure, following 400 mg single dose, under the fasted and fed states in healthy subjects are shown in FDA Table 65.

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FDA Figure 11. Simulated and observed plasma concentration-time profiles of ziftomenib on Cycle 1 Day 1 in patients with cancer

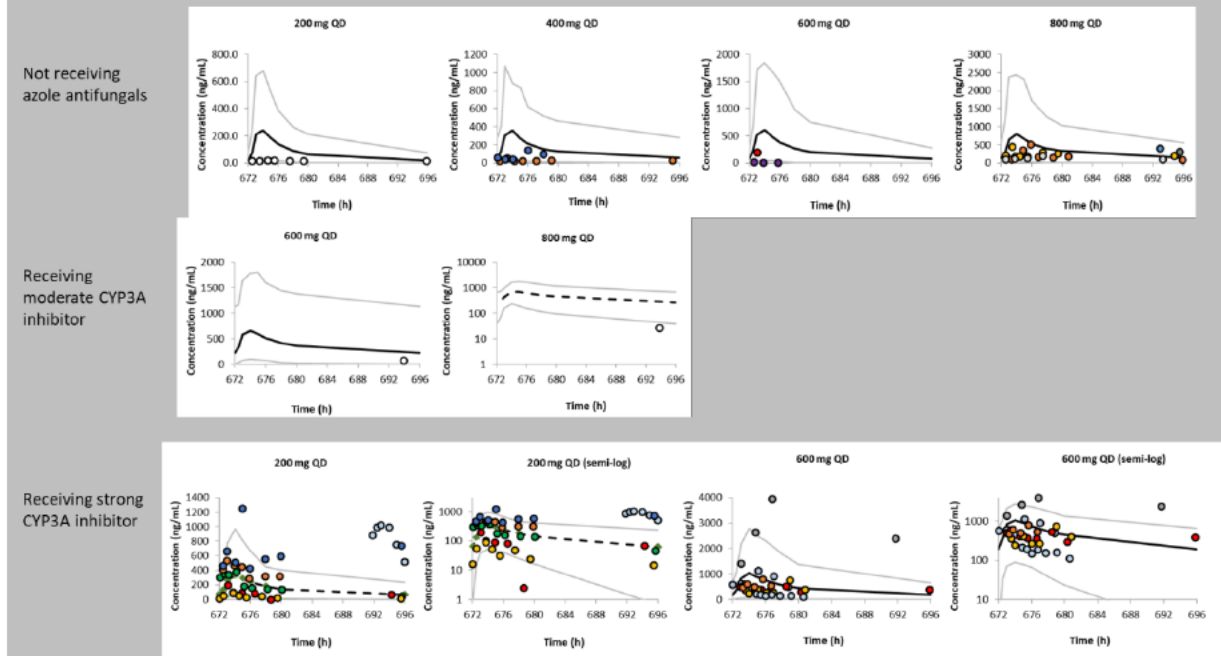


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FDA Figure 12. Simulated and observed plasma concentration-time profiles of ziftomenib on Cycle 2 Day 1 following once daily administration of ziftomenib in patients with cancer



Depicted are simulated (lines) and observed data (circles, clinical study KO-MEN-001). The dashed grey lines represent the 5th and 95th percentiles and the black line the mean data for the simulated population. Observed individual profiles are distinguished with different color symbols.

Source: Figures 1, 2 and 3 in the response-to-fda-clin-pharm-ir-dated-june-20-2025 (seq0018)

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FDA Table 63. Simulated and observed AUC and Cmax of ziftomenib in adult patients with cancer receiving ziftomenib once daily on Cycle 1 Day 1

Co-administered Drugs		No azole antifungals		Moderate CYP3A inhibitors		Strong CYP3A inhibitors	
Cohort		C1D1 AUC _{tau} (h.ng/mL)	C1D1 C _{max} (ng/mL)	C1D1 AUC _{tau} (h.ng/mL)	C1D1 C _{max} (ng/mL)	C1D1 AUC _{tau} (h.ng/mL)	C1D1 C _{max} (ng/mL)
200 mg QD	Simulated	405	69.4	480	69.7	688	94.7
	CV%	68.9	83.0	94.4	102	69.2	86.7
	Observed	51.9 (n=1)	3.29 (n=1)	296 (n=4)	31.7 (n=4)	616 (n=13)	67.5 (n=13)
	CV%	NA	NA	647	642	149	109
	S/O	7.80	21.1	1.62	2.20	1.12	1.40
400 mg QD	Simulated	596	81.7			1106	146
	CV%	85.9	128			119	123
	Observed	983 (n=2)	113 (n=2)			260 (n=2)	19.9 (n=2)
	CV%	372	166			51.0	120
	S/O	0.606	0.723			4.25	7.34
600 mg QD	Simulated	879	145	1297	160	2008	289
	CV%	99.4	127	101	120	100	124
	Observed	2110 (n=1)	199 (n=1)	1026 (n=2)	118 (n=2)	1744 (n=13)	142 (n=13)
	CV%	NA	NA	168	121	192	228
	S/O	0.417	0.729	1.26	1.36	1.15	2.04
800 mg QD	Simulated	2069	251	2737	228	4413	578
	CV%	1.10	134	63.8	70.9	155	170
	Observed	668 (n=1)	72.3 (n=1)	644 (n=3)	68.9 (n=3)	2892 (n=2)	195 (n=2)
	CV%	146	162	183	119	134	104
	S/O	3.10	3.47	4.25	3.31	1.53	2.96

Source: Tables 23, 24, and 25 in the PBPK report (ko-adme-0201-kur1g-pbpbk)

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FDA Table 64. Simulated and observed AUC and C_{max} of ziftomenib in adult patients with cancer receiving ziftomenib once daily on Cycle 2 Day 1

Co-administered Drugs		No azole antifungals		Moderate CYP3A inhibitors		Strong CYP3A inhibitors	
Cohort		C2D1 AUC _{tau} (h.ng/mL)	C2D1 C _{max} (ng/mL)	C2D1 AUC _{tau} (h.ng/mL)	C2D1 C _{max} (ng/mL)	C2D1 AUC _{tau} (h.ng/mL)	C2D1 C _{max} (ng/mL)
200 mg QD	Simulated	1062	182			2183	254
	CV%	119	127			107	102
	Observed	349 (n=1)	18.6 (n=1)			4037 (n=9)	338 (n=9)
	CV%	NA	NA			179	125
	S/O	3.04	9.78			0.541	0.751
400 mg QD	Simulated	1867	232	4990	467	3497	366
	CV%	154	189	149	143	207	170
	Observed	970 (n=2)	86.3 (n=2)	998 (n=1)	66.7 (n=1)	2460 (n=1)	122 (n=1)
	CV%	49.4	80.2	NA	NA	NA	NA
	S/O	1.92	2.69	5.00	7.00	1.42	3.00
600 mg QD	Simulated	2607	395			6268	740
	CV%	179	171			133	135
	Observed	13600 (n=1)	2500 (n=1)			9251 (n=9)	856 (n=9)
	CV%	NA	NA			145	92.4
	S/O	0.192	0.158			0.678	0.864
800 mg QD	Simulated	4008	519	7323	559	7706	969
	CV%	179	168	106	89.7	196	176
	Observed	5149 (n=5)	359 (n=5)	3437 (n=2)	151 (n=2)	20100 (n=1)	1120 (n=1)
	CV%	40.7	39.9	207	167	NA	NA
	S/O	0.778	1.45	2.13	3.70	0.383	0.865

Source: Tables 5A, 5B, and 5C in the response-to-fda-clin-pharm-ir-dated-july-28-2025 (seq0026)

FDA Table 65. Simulated and observed ziftomenib exposure under the fasted and fed states in healthy subjects

PK parameters	fasted				fed				food effect			
	C _{max} (ng/mL)	AUC _{0-inf} (ng*h/ml)	AUC ₀₋₁₂₀ (ng*h/ml)	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-inf} (ng*h/ml)	AUC ₀₋₁₂₀ (ng*h/ml)	T _{max} (h)	C _{max}	AUC _{0-inf}	AUC ₀₋₁₂₀	T _{max}
Simulated	192	2264	1630	1.80	590	8021	7980	3.65	3.07	3.54	4.90	2.03
Observed	123	2490	2250	3.00	502	10300	9670	5.00	4.08	4.14	4.30	1.67
Sim./Obs.	1.56	0.91	0.72	0.60	1.18	0.78	0.83	0.73	0.75	0.86	1.14	1.22

Source: Tables 6A and 6B in the response-to-fda-clin-pharm-ir-dated-july-28-2025 (seq0026)

Reviewer’s comments:

- Overall, the available PK data are insufficient for verifying model assumptions and ability of the ziftomenib PBPK model to predict its plasma concentration-time profiles and PK parameters in patients with cancer. The majority of the model-estimated AUC and C_{max} were beyond 2-fold of the observed values in patients who were taking ziftomenib at doses alone or co-administered with CYP3A inhibitors (FDA Table 63 and FDA Table 64). These large prediction errors may be due to: (1) sparse PK sampling, as

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some dose levels only had one blood sample (FDA Figure 12); (2) small sample size, as some dose levels only had PK data from one patient; (3) the PK parameters for ziftomenib were highly variable with CV% values up to 250%, which may be caused by high incidence of concomitant medications such as PPIs and weak CYP3A inducers besides CYP3A inhibitors.

- In the in vitro dissolution assay, ziftomenib capsules did not dissolve in the fed state media. This is inconsistent with the approximately 4-fold positive food effect observed in clinic (Study KO-MEN-003), indicating a disconnection between in vitro dissolution and in vivo performance in the fed state. In the modeling analysis for fed state simulation, ziftomenib was assumed not to precipitate, which was required to recover the positive food effect observed in Study KO-MEN-003. In other words, there is uncertainty about food effect prediction when clinical PK data are unavailable.

14.4.4.2. Effects of CYP3A precipitants on the PK of ziftomenib

The estimated effects of CYP3A inhibitors and inducers on the PK of ziftomenib following coadministration with 600 mg ziftomenib once daily for 29 days are summarized in FDA Table 66.

FDA Table 66. Geometric mean ratios of estimated PK parameters of ziftomenib in the absence and presence of CYP3A4 precipitants in patients with cancer

Classification of CYP3A DDI	CYP3A precipitants	Precipitant dosing regimens	Ziftomenib $f_{m,CYP3A}$			
			60%		70%	
			AUC _{tau} ratio	C _{max} ratio	AUC _{tau} ratio	C _{max} ratio
strong inhibitor	Itraconazole	200 mg QD	2.1	1.5	2.6	1.7
	Voriconazole	200 mg BID			2.5	1.7
		300 mg tablet BID on D1 then QD			2.4	1.6
		200 mg suspension TID			2.0	1.4
400 mg suspension BID	1.9	1.4				
moderate inhibitor	Fluconazole	200 mg QD	1.6	1.3	2.0	1.7
		400 mg QD			2.1	1.5
	Isavuconazole	372 mg Q8h equivalent			1.4	1.2
	Erythromycin	500 mg TID	1.5	1.3	1.7	1.3
weak inhibitor	Cimetidine	400 mg TID	1.4	1.2	1.4	1.2
strong inducer	Rifampin	600 mg QD	0.2	0.4	0.2	0.4
moderate inducer	Efavirenz	600 mg QD	0.3	0.5	0.3	0.4
weak inducer	Dexamethasone	8 mg BID	0.6	0.8	0.5	0.7

QD, once daily; BID, twice daily; TID, three times a day; Q8h, every 8 hours

Source: the response-to-fda-clin-pharm-ir- dated July 28, 2025 (seq0026)

Reviewer's comments:

To predict the effects of CYP3A inhibitors and inducers on ziftomenib PK, the fraction metabolized by CYP3A ($f_{m,CYP3A}$) is one of the key parameters that needs to be determined in the ziftomenib PBPK model. In the model development of ziftomenib, the fraction metabolized by CYP3A ($f_{m,CYP3A}$) value was optimized using the calculated differences in mean dose-adjusted

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AUC (2.3-fold) and C_{max} (2.0-fold) between patients who were taking ziftomenib on Cycle 1 Day 1 (C1D1) with and without co-administration of a strong CYP3A inhibitor (posaconazole or voriconazole). Additional sensitivity analysis determined that the $f_{m,CYP3A}$ value of 0.6 might be a more conservative estimate compared to the value of 0.5 though both could reproduce the calculated effects of strong CYP3A inhibitors. The model with the $f_{m,CYP3A}$ value of 0.6 predicted that a moderate CYP3A inhibitor such as fluconazole increased ziftomenib AUC and C_{max} 1.6- and 1.3-fold, respectively, whereas the calculated effects were 1.1-fold for AUC and 1.2-fold for C_{max} . As discussed in the Results section 1, the available PK data from the patients could not be used to adequately verify the $f_{m,CYP3A}$ value of ziftomenib.

Using data from in vitro reaction phenotyping, human mass balance and absolute bioavailability studies, in combination with Sensitivity Analysis, the reviewer estimated that an $f_{m,CYP3A}$ of 0.7 could be the worst case scenario: based on the metabolism studies conducted using recombinant CYP enzymes and isoform-selective chemical inhibitors with human liver microsomes (KO-ADME-0056), approximately 88-96% of ziftomenib metabolism was mediated by CYP3A4. In the human ADME study (KO-MEN-005), assuming 100% recovery of radioactivity, approximately 81% of the administered dose was identified as unchanged parent, and metabolites accounted for approximately 19% of the doses. The absolute bioavailability (BA) study (KO-MEN-005) determined the plasma clearance of ziftomenib (30.3 L/h) and the product (0.27) of intestinal availability (F_g) and fraction absorbed (f_a). Assuming low to no first-pass metabolism ($F_g \sim 0.8$ to 1), f_a was estimated to be 0.27 to 0.33, then the fraction metabolized (f_m) was estimated to be 0.56 to 0.70. Assuming that all the oxidative metabolites were properly identified in the human ADME study, the $f_{m,CYP3A}$ value of ziftomenib would range from 0.49 to 0.67, which is close to the optimized value discussed earlier. For evaluation of the potential worst-case scenario of DDIs, the Applicant was requested to simulate the effects of CYP3A inhibitors and inducers assuming a ziftomenib $f_{m,CYP3A}$ value of 0.7. The results are presented in FDA Table 66.

The Reviewer acknowledges, however, that there are several limitations of these estimated results: (1) in vitro, ziftomenib was determined to be a substrate of P-gp and BCRP and has low-to-moderate passive permeability (1.1×10^{-6} cm/s). In the BA study, as mentioned above, no more than 70% of the absorbed drug was metabolized, thus at least 30% of the drug was excreted as unchanged parent via the intestinal/ biliary route. Together with the low fraction absorbed of ziftomenib, these data indicate that we cannot dismiss a potential role of P-gp and BCRP in ziftomenib absorption and excretion, which was not considered in the estimated effects. (2) Population PK analysis showed that ziftomenib clearance in patients with cancer was 2.6-fold lower compared to healthy subjects. The mechanisms for this difference are unclear, thus this clearance difference was not considered in the estimation. The default cancer population model assumes that there is no difference in CYP3A abundance compared to the healthy population model. If the low clearance in the patient population was due to low CYP3A abundance in patients with cancer, then the potential effects of CYP3A inhibition would be overestimated. It should be noted that, for strong CYP3A inhibitors, the estimated effects were generally consistent with the population PK analysis, which showed the effects of strong CYP3A inhibitors

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on ziftomenib AUC ranging from 1.8- to 2.7-fold. For moderate or weak CYP3A inhibitors, however, population PK analyses showed no effects on ziftomenib exposure.

14.4.4.4.3. Effects of ziftomenib on the substrates of CYP3A, CYP2Cs and UGT1A1

Ziftomenib is expected to have a moderate inhibitory effect on the sensitive CYP3A substrate midazolam and have a minimal effect (AUC ratio <1.25) on the UGT1A1 substrate raltegravir and substrates of CYP2C isoforms in patients with cancer (FDA Table 67).

FDA Table 67. Predicted effects of ziftomenib on the substrates of CYP3A, CYP2C isoenzymes and UGT1A1 following oral administration of multiple doses of ziftomenib in patients with cancer

Substrates	K _{i,n} (μM)	K _{i,n} (μM)	AUC _{0-inf} GMR	C _{max} GMR
Midazolam (CYP3A4)	0.036	0.013	2.41 (2.16, 2.69)	1.48 (1.42, 1.55)
	0.0036	0.013	2.61 (2.32, 2.94)	1.55 (1.49, 1.62)
Raltegravir (UGT1A1)	0.070	NA	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)
	0.0070	NA	1.07 (1.06, 1.08)	1.08 (1.07, 1.09)
Repaglinide (CYP2C8)	0.412		1.23 (1.19, 1.27)	1.13 (1.11, 1.15)
	0.0412		1.24 (1.20, 1.28)	1.13 (1.12, 1.15)
S-Warfarin (CYP2C9)	0.190		1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
	0.0190		1.01 (1.01, 1.01)	1.00 (1.00, 1.00)
Omeprazole (CYP2C19)	0.224		1.18 (1.13, 1.24)	1.05 (1.05, 1.06)
	0.0224		1.21 (1.16, 1.27)	1.07 (1.06, 1.08)

A single dose of 5 mg midazolam, 0.25 mg repaglinide, 10 mg warfarin, 20 mg omeprazole, or 400 mg raltegravir was given on Day 11 following ziftomenib 600 mg QD* for 24 days.

*1400 mg QD dose of ziftomenib was used in the simulations so that the simulated steady state ziftomenib AUC (12560h*ng/mL) could match the higher exposure observed in patients with coadministration of a strong CYP3A inhibitor.

K_i values were calculated from in vitro IC₅₀ values using the Cheng-Prusoff equation. Simulations were also conducted using 10-fold lower K_i values.

Sources: Table 3 in Responses to FDA Clin Pharm IR dated July 28, 2025 (seq 0026)

Reviewer's comments:

- In the report KO-ADME-0201, the f_{u,mic} value was predicted based on a microsomal protein concentration of 0.05 mg/mL, 0.853 for the CYP3A inhibition experiments. The microsomal protein concentration was 0.25 mg/mL for the mechanism-based CYP3A inhibition study. In addition, the nonspecific binding in HLM was measured and reported in KO-ADME-0046. The measured f_{u,mic} values were approximately 0.04 at 0.1 mg/mL and 0.011 at 0.3 mg/mL, which are much lower than the predicted values. The Applicant was requested to recalculate the f_{u,mic} value for the simulation based on the actual microsomal concentration and measured f_{u,mic} value. The reported results in FDA Table 67 were simulated using a f_{u,mic} value of 0.04 for CYP3A4 K_i and 0.011 for CYP3A4 K_I.

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- Following administration of 600 mg ziftomenib QD, the steady state ziftomenib AUC and C_{max} in patients are 12200 h*ng/mL and 881 ng/mL (proposed ziftomenib label). However, the exposure of ziftomenib at the last dose in the simulated midazolam DDI study (simulation output file 'ir-06202025-38.xlsx') was 913 h*ng/mL for AUC and 124 ng/mL for C_{max} , which are more than 13- and 7-fold lower than those estimated from patients, respectively. The Applicant argued that the steady-state exposure of ziftomenib was calculated based on PK data from patients who were on posaconazole (strong CYP3A inhibitor) and should not be used to evaluate the effect of ziftomenib on midazolam exposure (Response to FDA Clin Pharm IR dated June 20, 2025, seq 0018). The reviewer disagrees. In the Phase 1/2 study (KO-MEN-001), 82% of cancer patients with NPM1-m were co-administered ziftomenib with strong CYP3A inhibitors, and the descriptive statistics of the steady-state exposure parameters of 600 mg ziftomenib in this population (N=94 out of 100 efficacy population and N=111 out of 119 safety population) were similar to the values in the proposed label (Table 11 and Table 12 in report KO-PK-0001). Therefore, the Applicant was requested to simulate the effect of ziftomenib on substrates of CYP3A, CYP2C isoenzymes, and UGT1A1 using the steady-state exposure of ziftomenib, and the results are presented in FDA Table 67. Of note, the population PK analysis estimated for steady state (C2D1) ziftomenib AUC and C_{max} in patients not receiving azoles were 5512 h*ng/ml and 288 ng/mL, which are also greater than the original Applicant's simulated exposure (reviewer's analysis). During the labeling negotiation, the Applicant performed an addition simulation and found that, at a ziftomenib AUC of 6220 *ng/ml, ziftomenib was predicted to increase the AUC and C_{max} of midazolam by up to 1.9- and 1.4-fold.
- The Applicant provided predictions of the effect of ziftomenib on the CYP3A substrate venetoclax. However, these predictions are considered exploratory (data not shown) since no documentation of venetoclax model development and verification was provided by the Applicant (Response to FDA Clin Pharm IR dated June 20, 2025, seq 0018).

14.4.4.4. Effects of staggered dosing of proton pump inhibitors on the exposure of ziftomenib

The Applicant proposed staggering dosing of a proton pump inhibitor (PPI) (administered 2-12 h after ziftomenib) to minimize its effect on decreasing ziftomenib exposure, as observed with rabeprazole (KO-MEN-003).

The PBPK analyses indicate that staggered dosing would not help minimize the interaction between PPIs (e.g., rabeprazole and esomeprazole) and ziftomenib for the following reasons:

- As illustrated in FDA Figure 13, at the Applicant's proposed ziftomenib administration time points, the gastric pH values (intersections of the blue vertical lines with the observed time courses of gastric pH on Day 7), are mostly above the pH value at which the effect of rabeprazole on ziftomenib was observed (intersection of the red vertical and horizontal lines). Therefore, PPIs are expected to have the same, if not greater, effects on ziftomenib exposure as that observed if ziftomenib is administered at these time points.

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- As shown in FDA Table 68, the predicted effects of esomeprazole on ziftomenib exposure were similar to the observed effects of rabeprazole on ziftomenib, when ziftomenib was administered 10, 12, and 14 h following multiple-dose administration of a PPI, indicating that staggered dosing did not help to minimize the interaction.
- The effect of esomeprazole on ziftomenib exposure was predicted to be minimal when the PPI was administered 2 h after ziftomenib administration, or when ziftomenib was administered 22 h after PPI administration, as indicated in FDA Table 68. However, we note that the PBPK analyses underpredicted the observed effect of rabeprazole on ziftomenib AUC by approximately 34% following once daily dosing of 10 mg rabeprazole for 5 days (FDA Table 68). This underprediction may result from the lower simulated pH compared to the observed and the pK_a value of ziftomenib (FDA Figure 13). Ziftomenib is a poorly soluble weak base with pK_a values of 8.2 and 4.78. Its ionization properties around pH 4.78 are expected to significantly affect its pharmacokinetics. The dynamic pH model failed to capture the nocturnal rise of gastric pH, and the simulated pH values were below the observed gastric pH and/or the pK_a value of ziftomenib after 12 h of PPI administration (FDA Figure 13). Therefore, the effects of esomeprazole on ziftomenib exposure may be also underestimated if ziftomenib is administered 14 h or 22 h after esomeprazole administration.
- The ziftomenib PBPK model failed to describe the ziftomenib plasma concentration-time profiles and did not capture its absorption phase in the absence of CYP3A inhibitors in cancer patients (FDA Figure 12).

Taken together, the PBPK analyses do not support staggered dosing of PPIs to minimize the effects of PPIs on ziftomenib exposure.

FDA Table 68. Simulated and observed effects of proton pump inhibitors on ziftomenib exposure

Ziftomenib and PPI dosing regimens	Timing of PPI dosing relative to ziftomenib	Ziftomenib		Ziftomenib + PPI		GMR	
		AUC _{τ/inf}	C _{max}	AUC _{τ/inf}	C _{max}	AUC _{τ/inf}	C _{max}
ZFM 400 mg SD rabeprazole QD	2h before (obs.)	2490	123	1170	37.4	0.47	0.3
	2h before (sim.)	2403	211	1490	50.4	0.63	0.24
Ziftomenib 600 mg QD + esomeprazole QD 14d	2h after	2871	465	2280	365	0.79	0.79
	10h before	2871	465	1077	156	0.38	0.34
	12h before	2871	465	1357	205	0.47	0.44
	14h before	2871	465	1626	252	0.57	0.54

Obs, observed; sim, simulated; sd, single dose; QD, Once daily dosing; d, day; PPI, proton pump inhibitor; AUC_{τ/inf}, area under the plasma concentration-time curve during a dosing interval or from 0 to infinity; C_{max}, peak plasma concentration.

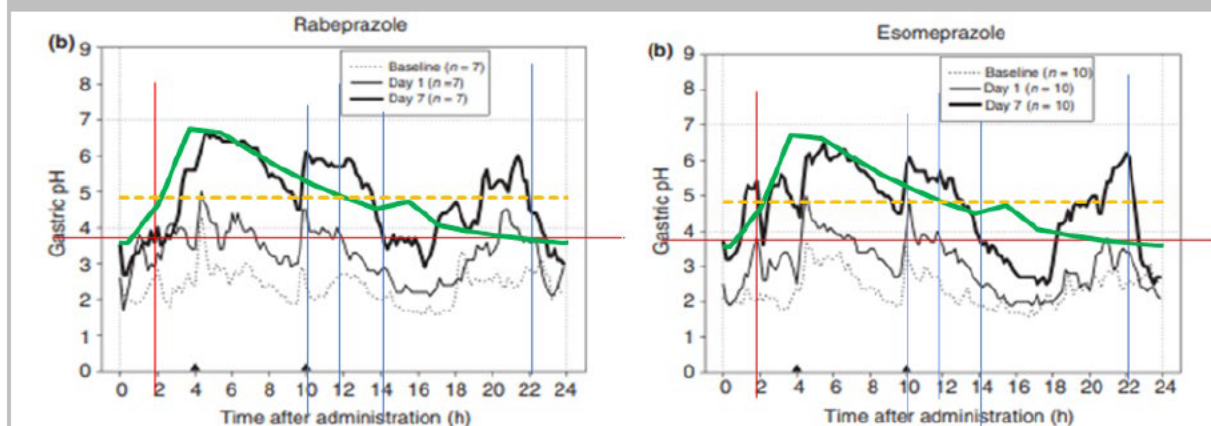
Source: Responses to FDA Clin Pharm IR dated July 28, 2025 (seq 0026)

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FDA Figure 13. Simulated and observed time courses of gastric pH over 24 hours following once daily PPI administration for seven days



The intersection of the red vertical and horizontal lines approximates the pH at which the effect of rabeprazole on ziftomenib was observed. The blue vertical lines represent the Applicant's proposed ziftomenib dosing times after PPI administration. The green line is the simulated time course of pH following oral administration of 20 mg esomeprazole once daily for 7 days (Responses to FDA Clin Pharm IR dated July 28, 2025). The yellow dashed line represents the pK_a of ziftomenib. The observed time courses of gastric pH are published by Sakurai et al (PMID: 26193978).

Source: Adapted from Sakurai et al (PMID: 26193978) by the reviewer and Responses to FDA Clin Pharm IR dated July 28, 2025 (seq 0026)

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14.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

FDA conducted additional safety analysis as noted above. FDA grouped similar preferred terms into the following FDA group terms based on MEDRA hierarchy or grouping shown in FDA Table 69 below. Actual PTs mapped from the ISS into these group terms are shown in FDA Table 70.

FDA Table 69. FDA Grouped Terms Used for FDA Analyses of Adverse Events, by Basis for Term

Grouped Term	Basis for Grouped Term
Abdominal pain	HLT Gastrointestinal and abdominal pains (excl oral and throat)
Bacterial infection	HLGT Bacterial infectious disorders, PT Bacteraemia
Cardiac Failure	HLGT Heart failures, HLGT Myocardial disorders, PTs Ejection fraction decreased,
Cough	HLT Coughing and associated symptoms
Depressed level of consciousness	HLT Disturbances in consciousness NEC
Diarrhoea	HLT Diarrhoea (excl infective), HLT Colitis (excl infective)
Drug hypersensitivity	AETERM
Dyspnoea	HLT Breathing abnormalities
Face oedema	AETERM, swelling face
Fatigue	HLT Asthenic conditions
Fungal infection	HLGT Fungal infectious disorders, PT Aspergilloma
Haemorrhage	Haemorrhage terms (excl laboratory terms) (SMQ)
Headache	HLGT Headaches
Hyperbilirubinaemia	HLT Cholestasis and jaundice, PT Blood bilirubin increased, Bilirubin conjugated increased
Hypertension	Hypertension (SMQ)
Hypotension	HLT Vascular hypotensive disorders
Infection	HLGT Infections - pathogen unspecified
Leukocytosis	PTs Hyperleukocytosis, Leukocytosis, White blood cell count increased
Musculoskeletal pain	HLT Muscle pains, HLT Musculoskeletal and connective tissue pain and discomfort, PT Arthralgia, Bone pain
Nausea	HLT Nausea and vomiting symptoms
Neuropathy peripheral	HLGT Peripheral neuropathies,
Oedema	HLT Oedema NEC, PT Peripheral swelling
Paraesthesia	HLT Paraesthesias and dysaesthesias
Rash	HLT Rashes, eruptions and exanthems NEC, HLT Bullous conditions, HLT Exfoliative conditions, HLT Dermatitis ascribed to specific agent
Renal impairment	HLT Renal failure and impairment, HLT Renal function analyses, HLT Renal failure complications
Stomatitis	HLT Stomatitis and ulceration
Tachycardia	PTs Tachycardia, Atrial tachycardia, Sinus tachycardia, Atrial fibrillation, ventricular tachycardia

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Taste disorder	PTs Ageusia, Dysgeusia, , Taste disorder
Thrombosis	Embolitic and thrombotic events (SMQ) peripheral ischemia. (did not include DIC (included under haemorrhage) or stress cardiomyopathy (included under cardiac failure))
Transaminases increased	PTs Hypertransaminaemia Alanine aminotransferase Alanine aminotransferase increased Aspartate aminotransferase increased Gamma-glutamyltransferase Transaminases increased
Viral infection	HLGT Viral infectious disorders, PT cytomegalovirus viraemia, Epstein-Barr virus infection, Gastroenteritis norovirus, Norovirus infection, Respiratory syncytial virus infection, Sapovirus infection
Visual impairment	HLT Visual disorders NEC, HLT Visual impairment and blindness (excl colour blindness)

FDA Table 70. FDA Grouped Terms Used for FDA Analyses of Adverse Events, by Preferred Term (PT)

Grouped Term	PTs Comprising FDA Grouped Term
Abdominal pain	Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness
Bacterial infection	Anorectal cellulitis, Bacteraemia, Bacterial infection, Bacterial pyelonephritis, Bacterial sepsis, Breast cellulitis, Capnocytophaga infection, Cellulitis, Clostridial infection, Clostridium bacteraemia, Clostridium colitis, Clostridium difficile colitis, Clostridium difficile infection, Enterobacter sepsis, Enterococcal bacteraemia, Enterococcal infection, Enterocolitis bacterial, Erysipelas, Escherichia bacteraemia, Escherichia infection, Escherichia sepsis, Escherichia urinary tract infection, External ear cellulitis, Folliculitis, Klebsiella bacteraemia, Klebsiella infection, Klebsiella urinary tract infection, Paronychia, Periorbital cellulitis, Pneumonia bacterial, Pneumonia klebsiella, Pseudomonas bacteraemia, Staphylococcal bacteraemia, Staphylococcal infection, Stenotrophomonas infection, Streptococcal bacteraemia, Streptococcal infection, Urinary tract infection enterococcal, Vulval cellulitis, Klebsiella sepsis, Stomatococcal infection
Cardiac Failure	Cardiac failure, Cardiomyopathy, Ejection fraction decreased, Myocardial injury, Myocarditis, Stress cardiomyopathy
Cough	Cough, Productive cough
Depressed level of consciousness	Lethargy, Somnolence, Syncope
Diarrhoea	Colitis, Colitis erosive, Colitis ischaemic, Diarrhoea, Neutropenic colitis
Drug hypersensitivity	AETERM
Dyspnoea	Dyspnoea, Dyspnoea exertional, Respiratory distress, Tachypnoea
Face oedema	Face oedema, Swelling face
Fatigue	Asthenia, Fatigue, Malaise
Fungal infection	Aspergilloma, Bronchopulmonary aspergillosis, Candida infection, Candida pneumonia, Fungal infection, Fusarium infection, Onychomycosis, Oral candidiasis, Oropharyngeal candidiasis, Pneumonia fungal, Sinusitis fungal, Skin candida, Tinea pedis, Vulvovaginal mycotic infection
Haemorrhage	Angina bullosa haemorrhagica, Bladder tamponade, Breast haematoma, Catheter site haematoma, Catheter site haemorrhage, Cerebral haematoma, Conjunctival haemorrhage, Contusion, Disseminated intravascular coagulation, Ecchymosis, Epistaxis, Gastric haemorrhage, Gastrointestinal

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	haemorrhage, Gingival bleeding, Haematemesis, Haematochezia, Haematoma, Haematospermia, Haematuria, Haemoptysis, Haemorrhage, Haemorrhage intracranial, Haemorrhoidal haemorrhage, Heavy menstrual bleeding, Hyperfibrinolysis, Injection site haematoma, Injection site haemorrhage, Lower gastrointestinal haemorrhage, Melaena, Mouth haemorrhage, Oral blood blister, Petechiae, Post procedural haemorrhage, Postmenopausal haemorrhage, Pulmonary alveolar haemorrhage, Purpura, Rectal haemorrhage, Retinal haemorrhage, Shock haemorrhagic, Skin haemorrhage, Subdural haematoma, Subdural haemorrhage, Tongue haemorrhage, Traumatic haematoma, Upper gastrointestinal haemorrhage, Vaginal haemorrhage, Vitreous haemorrhage
Headache	Headache
Hyperbilirubinaemia	Bilirubin conjugated increased, Blood bilirubin increased, Cholestasis, Hyperbilirubinaemia, Jaundice cholestatic
Hypertension	Hypertension
Hypotension	Hypotension, Orthostatic hypotension
Infection	Abdominal abscess, Abdominal infection, Abscess limb, Acute sinusitis, Anal abscess, Anorectal infection, Appendicitis, Bronchitis, Conjunctivitis, Dermo-hypodermatitis, Device related infection, Device related sepsis, Diverticulitis, Ear infection, Emphysematous cystitis, Endocarditis, Enterocolitis infectious, Epiglottitis, Eye infection, Gingivitis, Hepatic infection, Hordeolum, Infection, Kidney infection, Large intestine infection, Lip infection, Liver abscess, Nail infection, Necrotising fasciitis, Orchitis, Otitis media, Penile infection, Pericoronitis, Periodontitis, Perirectal abscess, Peritonitis, Pharyngitis, Pneumonia, Pneumonia aspiration, Postoperative abscess, Rash pustular, Rectal abscess, Respiratory tract infection, Rhinitis, Sepsis, Septic shock, Sinusitis, Skin infection, Soft tissue infection, Splenic infection, Stoma site infection, Tongue abscess, Tooth infection, Upper respiratory tract infection, Urosepsis, Vaginal infection, Vascular device infection, Wound infection
Leukocytosis	Hyperleukocytosis, Leukocytosis, White blood cell count increased
Musculoskeletal pain	Bone pain, Arthralgia, Back pain, Flank pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain, Pain in extremity
Nausea	Cannabinoid hyperemesis syndrome, Nausea, Vomiting
Neuropathy peripheral	Neuropathy peripheral, Peripheral sensory neuropathy
Oedema	Generalised oedema, Localised oedema, Oedema, Oedema peripheral, Peripheral swelling
Paraesthesia	Dysaesthesia, Hyperaesthesia, Hypoaesthesia, Paraesthesia
Rash	Bullous haemorrhagic dermatosis, Dermatitis, Dermatitis bullous, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Eczema, Erythema multiforme, Hand dermatitis, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash popular, Rash pruritic, Seborrhoeic dermatitis, Skin exfoliation
Renal impairment	Acute kidney injury, Azotaemia, Blood creatinine increased, Blood urea increased, Chronic kidney disease, Postrenal failure, Renal failure
Stomatitis	Aphthous ulcer, Mouth ulceration, Stomatitis
Tachycardia	Atrial fibrillation, Sinus tachycardia, Supraventricular tachycardia, Tachycardia, Ventricular tachycardia
Taste disorder	Ageusia, Dysgeusia, Taste disorder
Thrombosis	Atrial thrombosis, Cardiac ventricular thrombosis, Central venous catheterization, Cerebral ischaemia, Cerebrovascular accident, Deep vein thrombosis, Device related thrombosis, Embolism, Jugular vein thrombosis,

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	Myocardial infarction, Peripheral embolism, Peripheral ischaemia, Splenic infarction, Thrombophlebitis, Thrombosis, Thrombosis in device
Transaminases increased	Hypertransaminaemia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase Transaminases increased
Viral infection	Adenovirus infection, COVID-19, COVID-19 pneumonia, Cytomegalovirus infection reactivation, Cytomegalovirus viraemia, Enterovirus infection, Epstein-Barr virus infection, Gastroenteritis norovirus, Genital herpes, Herpes simplex reactivation, Herpes virus infection, Herpes zoster, Influenza, Metapneumovirus infection, Metapneumovirus pneumonia, Nasal herpes, Norovirus infection, Oral herpes, Parainfluenzae virus infection, Pneumonia cytomegaloviral, Pneumonia influenzal, Pneumonia parainfluenzae viral, Pneumonia respiratory syncytial viral, Respiratory syncytial virus infection, Rhinovirus infection, Sapovirus infection, Viral upper respiratory tract infection
Visual impairment	Blindness unilateral, Diplopia, Vision blurred, Visual acuity reduced, Visual impairment

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15 Division Director (DHM1)

X

Director (Acting), Division of Hematological Malignancies 1 (DHM1)

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16 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

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DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Nonclinical Reviewer	Simon Williams, PhD	OOD/DHOT	Sections: 5	X Authored Approved
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Nonclinical Deputy Division Director	Tiffany Ricks, PhD	OOD/DHOT	Sections: 5	Authored X Approved
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Clinical Pharmacology Reviewer	Morgan Butrovich, PhD, Pharm D	OCP/DCPI	Sections: 6, 14	X Authored Approved
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Clinical Pharmacology Team Leader	Xiling Jiang, Pharm D	OCP/DCPI	Sections: 6, 14	Authored X Approved
	Signature: Xiling Jiang -S Digitally signed by Xiling Jiang -S Date: 2025.10.08 16:14:04 -04'00'			
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 14	Authored X Approved
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Pharmacogenomics Reviewer	Javier Blanco, PhD	OCP/DPM	Sections: 6	X Authored Approved
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DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
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Statistical Reviewer	Xin Wang, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	X Authored Approved
	Signature: Xin Wang -S Digitally signed by Xin Wang -S Date: 2025.10.03 15:47:31 -04'00'			
Statistical Team Leader	Jonathan Vallejo, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	Authored X Approved
	Signature: JONATHON J. VALLEJO -S Digitally signed by JONATHON J. VALLEJO -S Date: 2025.11.03 14:50:05 -05'00'			
Division Director (OB) designee	Yuan Li Shen, DrPH	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	Authored X Approved
	Signature: YUAN-LI SHEN -S Digitally signed by YUAN-LI SHEN -S Date: 2025.11.03 14:38:24 -05'00'			
Clinical Reviewer	Joseph Wynne, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10, 14	X Authored Approved
	Signature: Joseph P. Wynne -S Digitally signed by Joseph P. Wynne -S Date: 2025.11.03 13:42:08 -05'00'			

NDA Multidisciplinary Review and Evaluation

NDA 220305

Komzifti (ziftomenib)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Clinical Team Leader	Cara Rabik, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10, 14	Authored X Approved
	Signature: Cara A. Rabik -S Digitally signed by Cara A. Rabik -S Date: 2025.11.03 15:11:45 -05'00'			
Associate Director for Labeling	Evan Bryson, PharmD	OOD	Sections: 11	X Authored Approved
	Signature: Evan B. Bryson -S Digitally signed by Evan B. Bryson -S Date: 2025.10.07 14:27:46 -04'00'			
Cross-Discipline Team Leader	Cara Rabik, MD, PhD	OOD/DHMI	Sections: 1, 4, 5, 12, 13	X Authored Approved
	Signature: <i>{See appended electronic signature page}</i>			
Division Director (Acting) (Clinical)	Kelly Norsworthy, MD	OOD/DHMI	Sections: All	Authored X Approved
	Signature: <i>{See appended electronic signature page}</i>			
Office Director (or designee)	R. Angelo de Claro, MD	OOD	Sections: All	Authored X Approved
	Signature: <i>{See appended electronic signature page}</i>			

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

/s/

CARA A RABIK
11/12/2025 03:35:43 PM

KELLY J NORSWORTHY
11/12/2025 03:55:59 PM

ROMEO A DE CLARO
11/13/2025 09:12:51 AM