Pharmacokinetic (PK) Assessment of Revumenib in Patients With Relapsed/Refractory (R/R) Acute Leukemias Harboring a *KMT2A* Rearrangement (*KMT2A*r) or *NPM1* Mutation (*NPM1*m): Impact of Food and Concomitant Medications

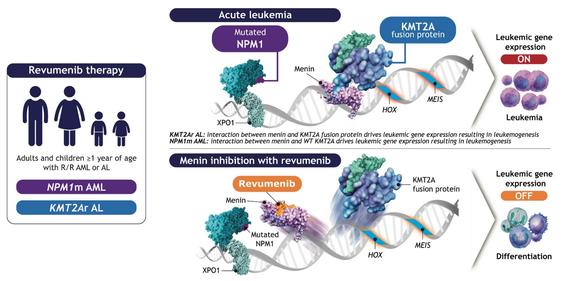
PF564

Enoch Cobbina,[1] Joshua Stewart,[1] YuWei Lin,[2] Angela R. Smith,[1] Ophelia Yin,[1] Ghayas C. Issa[3]
[1]Syndax Pharmaceuticals, Inc., New York, NY; [2]Certara Drug Development Solutions, Princeton, NJ; [3]The University of Texas MD Anderson Cancer Center, Houston, TX.

INTRODUCTION

- Revumenib, a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction (**Figure 1**), is used for the treatment of relapsed/refractory (R/R) acute myeloid leukemia harboring an ***NPM1* mutation** (*NPM1*m) or R/R acute leukemia with a ***KMT2A* translocation** in adult and pediatric patients 1 year and older[1,2]
- Given the severity of disease, frequent polypharmacy, and variable clinical status in patients with R/R acute leukemias,[3-6] dosing flexibility is essential to support consistent treatment delivery and optimize outcomes

Figure 1. Revumenib mechanism of action



HOX, homeobox; *MEIS*, Meis homeobox.

OBJECTIVE

- To characterize the pharmacokinetics (PK) of revumenib and its major metabolite (M1), with emphasis on factors that may influence dosing flexibility, including food and concomitant medications (such as CYP3A4 inhibitors [CYP3A4i]) and gastric acid-reducing agents (such as antacids, histamine 2 receptor antagonists [H2RAs], and proton pump inhibitors [PPIs])

METHODS

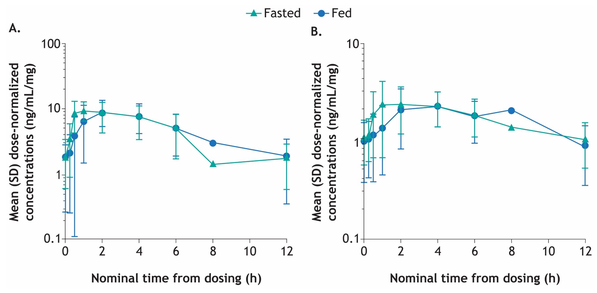
- PK data were obtained from 286 adult (≥18 years of age) and 49 pediatric (<18 years of age) patients with acute leukemia, including those with *KMT2A* rearrangements (*KMT2A*r) and *NPM1*m, who were enrolled in the phase 1/2 AUGMENT-101 trial (NCT04065399) following single and multiple doses of revumenib
- For the food-effect assessment, noncompartmental PK analyses were performed in a subgroup of patients (n = 11) who received revumenib in a fasted state and after the intake of a low-fat meal
- For concomitant medication assessment, population PK (PopPK) modeling was conducted using data from all patients to systematically quantify PK variability and evaluate these covariate effects
- Measured PK parameters included maximum concentration (C_{max}), area under the concentration-time curve (AUC), time to C_{max} (T_{max}), C_{max} at steady state ($C_{max,ss}$), minimum concentration at steady state ($C_{min,ss}$), and AUC at steady state (AUC_{ss}) for revumenib and M1

RESULTS

Food effects

- Revumenib and M1 exposure ranges overlapped under fasted and fed (low-fat meal) conditions (**Figure 2**)
- As compared with the fasted state, a low-fat meal (400-500 calories with ≤25% fat content) reduced revumenib C_{max} and AUC by 27% and 12%, respectively, and M1 C_{max} and AUC by 14% and 18%, respectively. Median T_{max} was unchanged for revumenib and delayed by 1.8 hours for M1 (**Table 1**)

Figure 2. Mean (SD) plasma concentration-time profiles of (A) revumenib and (B) M1 under fasted or fed (low-fat meal) conditions



M1, major metabolite of revumenib; SD, standard deviation.

Table 1. Summary of dose-normalized PK parameters of revumenib and M1 under fasted or fed (low-fat meal) conditions

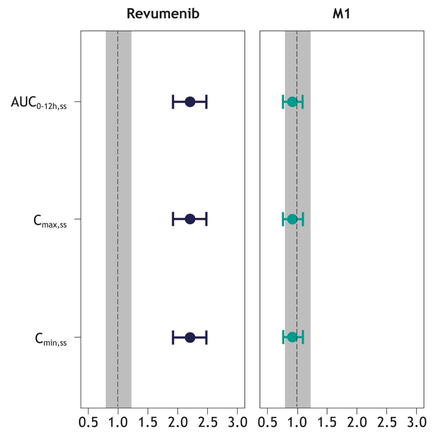
Analyte	Parameter	Units	Fasted[a]	Fed[a]	Geometric mean ratio (90% CI) Fed vs Fasted
Revumenib	DN_C_{max}	ng/mL/mg	11.99 (26.6); 11	8.715 (51.8); 11	72.61 (52.37, 100.68)
	DN_$AUC_{0\text{-}6h}$	ng·h/mL/mg	42.02 (34.3); 11	34.20 (64.3); 11	81.47 (60.52, 109.67)
	DN_$AUC_{0\text{-}12h}$	ng·h/mL/mg	119.2 (42.8); 11	101.7 (62.5); 9	87.69 (67.06, 114.66)
	T_{max}	h	2.00 (0.48-4.13); 11	2.13 (2.00-4.20); 11	NA
M1	DN_C_{max}	ng/mL/mg	2.401 (60.1); 11	2.080 (59.3); 11	86.31 (61.21, 121.7)
	DN_$AUC_{0\text{-}6h}$	ng·h/mL/mg	10.90 (49.7); 11	9.271 (58.7); 11	84.99 (60.9, 118.61)
	DN_$AUC_{0\text{-}12h}$	ng·h/mL/mg	37.29 (44.9); 11	30.78 (60.3); 10	81.83 (59.87, 111.86)
	T_{max}	h	2.00 (0.50-6.03); 11	3.83 (2.00-6.03); 11	NA

[a]Parameter values shown as geometric mean (geometric CV%); n. T_{max} presented as median (min-max); n.
CV, coefficient of variation; DN_$AUC_{0\text{-}6h}$, dose-normalized area under the concentration-time curve from time 0 to 6 hours post dose; DN_$AUC_{0\text{-}12h}$, dose-normalized area under the concentration-time curve from time 0 to 12 hours post dose; DN_C_{max}, dose-normalized maximum concentration; M1, major metabolite of revumenib; NA, not applicable; PK, pharmacokinetics; T_{max}, time to maximum concentration.

Effect of concomitant CYP3A4i

- PopPK modeling showed that co-administration with a strong CYP3A4i, such as voriconazole, posaconazole, and itraconazole, resulted in a 2.2-fold increase in revumenib $AUC_{0\text{-}12h,ss}$, $C_{max,ss}$, and $C_{min,ss}$, while M1 exposure was not affected (**Figure 3**)
- Co-administration with a moderate CYP3A4i, such as fluconazole and isavuconazole, did not show a meaningful effect on the exposures of revumenib or M1 (data not shown)

Figure 3. Forest plot showing the effect of strong CYP3A4i on steady-state exposure of revumenib and M1

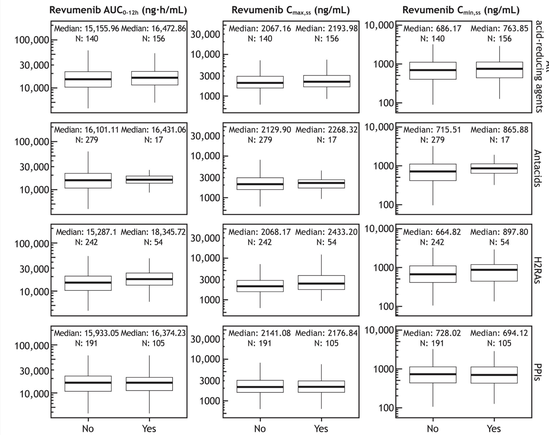


Gray shaded region represents a range of 0.8 to 1.25. Horizontal bars represent geometric mean and 90% CI for each parameter.
$AUC_{0\text{-}12h,ss}$, area under the concentration-time curve from time 0 to 12 hours at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; CYP3A4i, cytochrome P450 3A4 inhibitor; M1, major metabolite of revumenib.

Effect of concomitant antacids, H2RAs, and PPIs

- In AUGMENT-101, 52.7% of patients received gastric acid-reducing agents, with PPIs being most common (PPIs [35.5%], H2RAs [18.2%], antacids [5.7%])
- PopPK modeling showed no statistically significant effect of these concomitant medications on any revumenib PK parameters, with comparable revumenib exposures between patients who did and did not receive these agents (**Figure 4**); similar findings were observed for M1
- The absence of a meaningful drug-drug interaction effect aligns with the high solubility of revumenib across the physiologic pH range (1.2-6.8) as defined by the Biopharmaceutics Classification System

Figure 4. Predicted steady-state exposures of revumenib in patients who did and did not receive gastric acid-reducing agents



Data presented are PopPK model-predicted exposures at steady state following administration of revumenib 270 mg q12h without CYP3A4i. No: did not receive gastric acid-reducing agents; Yes: received gastric acid-reducing agents.
$AUC_{0\text{-}12h}$, area under the concentration-time curve from time 0 to 12 hours; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; CYP3A4i, cytochrome P450 3A4 inhibitor; H2RA, histamine 2 receptor antagonist; PopPK, population pharmacokinetics; PPI, proton pump inhibitor; q12h, every 12 hours.

CONCLUSIONS

- Low-fat meals did not cause clinically meaningful changes in revumenib or M1 PK, which indicates that revumenib can be administered under a fasted state or with a low-fat meal
- Revumenib can be dose adjusted to enable co-administration with a strong CYP3A4i
- Revumenib has no drug-drug interaction with antacids, H2RAs, or PPIs, which enables concomitant use of revumenib with these gastric acid-reducing agents
- Overall, these findings reinforce the flexible administration and individualized dosing provided by revumenib

REFERENCES

1. Issa GC, et al. *J Clin Oncol*. 2025;43(1):75-84.
2. Arellano ML, et al. *Blood*. 2025;146(9):1065-1077.
3. Ranieri R, et al. *Leukemia*. 2022;36(10):2351-2367.
4. Issa GC, et al. *Blood Cancer J*. 2021;11(9):162.
5. Li J, et al. *Cancer Chemother Pharmacol*. 2019;84(4):799-807.
6. Döhner H, et al. *Blood*. 2022;140(12):1345-1377.

ACKNOWLEDGMENTS

AUGMENT-101 is sponsored by Syndax Pharmaceuticals, Inc. Editorial and graphical assistance were provided by Alex Dimitri, PhD, of Lumanity Communications Inc., and were funded by Syndax Pharmaceuticals, Inc.

Previously presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; 29 May-02 Jun 2026; Chicago, IL, USA.