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

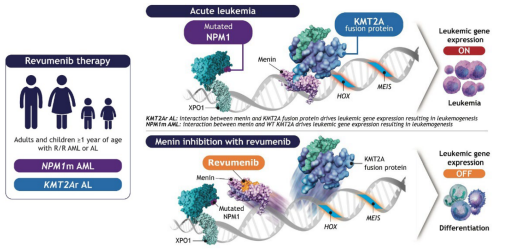
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INTRODUCTION

- 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

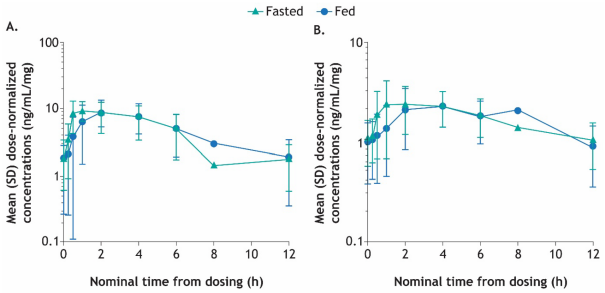
- PK data were obtained from 286 adult (≥18 years of age) and 49 pediatric (<18 years of age) patients with acute leukemia, including those with *KMT2A* rearrangements (*KMT2A*r) and *NPM1*m, who were enrolled in the phase 1/2 AUGMENT-101 trial (NCT04065399) following single and multiple doses of revumenib
- 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 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

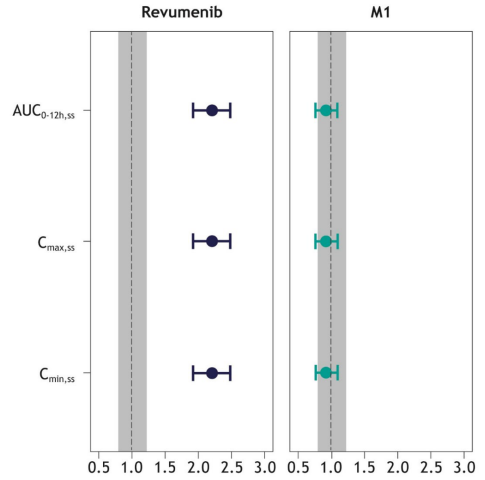
Analyte	Parameter	Units	Fasted[a]	Fed[a]	Geometric mean ratio (90% CI) Fed vs Fasted
Revumenib	DN_C_{max}	ng/mL/mg	11.99 (26.6); 11	8.715 (51.8); 11	72.61 (52.37, 100.68)
	DN_AUC_{0-6h}	ng·h/mL/mg	42.02 (34.3); 11	34.20 (64.3); 11	81.47 (60.52, 109.67)
	DN_AUC_{0-12h}	ng·h/mL/mg	119.2 (42.8); 11	101.7 (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_{0-6h}	ng·h/mL/mg	10.90 (49.7); 11	9.271 (58.7); 11	84.99 (60.9, 118.61)
	DN_AUC_{0-12h}	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_{0-6h}, dose-normalized area under the concentration-time curve from time 0 to 6 hours post-dose; DN_AUC_{0-12h}, 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 $AUC_{0-12h,ss}$, $C_{max,ss}$, 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

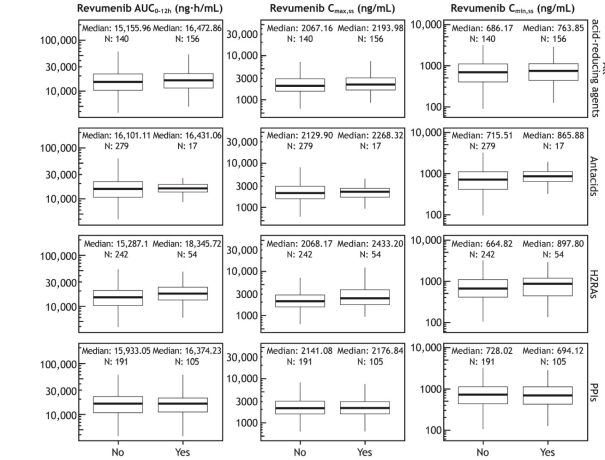


Gray shaded region represents a range of 0.8 to 1.25. Horizontal bars represent geometric mean and 90% CI for each parameter.
$AUC_{0-12h,ss}$, area under the concentration-time curve from time 0 to 12 hours at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; CYP3A4i, CYP3A4 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. $AUC_{0-\tau}$, 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, CYP3A4 inhibitor; H2RA, histamine 2 receptor antagonist; PopPK, population pharmacokinetics; PPI, proton pump inhibitor; q12h, every 12 hours.

CONCLUSIONS

- Low-fat meals do 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

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