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Population Pharmacokinetics (PopPK) of Revumenib in Patients with Relapsed/Refractory Acute Leukemias

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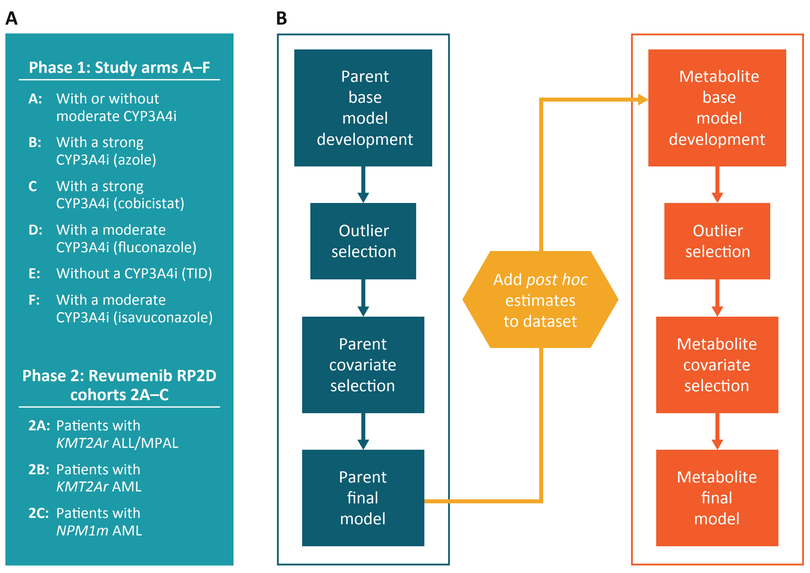
PURPOSE

- Revumenib, a selective, oral small-molecule inhibitor of the menin-lysine methyltransferase 2A (KMT2A) interaction is being investigated for the treatment of *KMT2A*-rearranged or *NPM1*-mutated relapsed/refractory acute leukemias
- The clinical pharmacology of revumenib has been determined in clinical studies and through model-based approaches
- Here, a population pharmacokinetic (PopPK) model for revumenib and its metabolite (M1) was developed using data from adult and pediatric patients from the phase 1/2 AUGMENT-101 study (NCT04065399)[1] to assess the effects of potential covariates on revumenib and M1 PK

METHODS

- Overall, physiologically based PK (PBPK), PopPK, and exposure–response efficacy and safety models were developed to determine or justify doses of revumenib and assess drug–drug interactions (DDI)
  - For this PopPK analysis, a sequential parent–metabolite PK modeling approach was utilized (**Figure 1**)
- Monte Carlo simulations in 1000 virtual patients were conducted to justify the revumenib dose/regimen when administered with and without strong cytochrome P450 3A4 inhibitors (CYP3A4i)

Figure 1. AUGMENT-101 (A) study design and (B) sequential parent–metabolite PopPK modeling approach



Revumenib was administered orally every 12 hours or TID in a 28-day cycle via capsule, tablet, or oral solution.
ALL, acute lymphoblastic leukemia; **AML**, acute myeloid leukemia; **CYP3A4i**, cytochrome P450 3A4 inhibitor; ***KMT2Ar***, lysine methyltransferase 2A rearrangements; **MPAL**, mixed phenotype acute leukemia; ***NPM1m***, nucleophosmin 1 mutated; **PopPK**, population pharmacokinetics; **TID**, three times daily.

RESULTS

- A total of 251 patients had evaluable PK data, comprising 4869 plasma concentration samples
- Key baseline and time-varying covariates are summarized in **Table 1**

Table 1. Summary of baseline and time-varying covariates

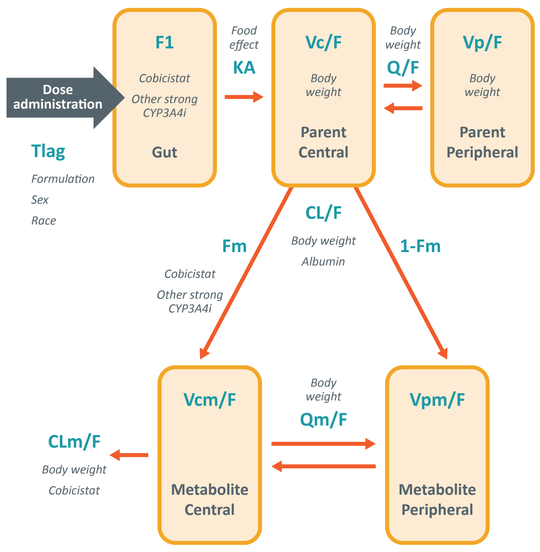
Baseline covariate	Statistic/value	Patients (N=251)
Age, years	Mean (SD)	42.6 (22.8)
	Median (range)	42.0 (0.75–82.0)
Age category, n (%)	1 month to <2 years	7 (2.8)
	2 to <6 years	14 (5.6)
	6 to <12 years	9 (3.6)
	12 to <18 years	13 (5.2)
	≥18 years of age	208 (82.9)
Body weight, kg	Mean (SD)	68.4 (26.9)
	Median (range)	69.8 (8.1–146.0)
Time-varying covariate	**Statistic/value**	**Patients[a]**
Concomitant weak CYP3A4i (n=271), n (%)	No	193 (71.2)
	Yes	78 (28.8)
Concomitant moderate CYP3A4i (n=261), n (%)	No	227 (87.0)
	Yes	34 (13.0)
Concomitant strong CYP3A4i (n=300), n (%)	Without strong CYP3A4i[b]	106 (35.3)
	With cobicistat	37 (12.3)
	With other strong CYP3A4i	154 (51.3)
	With cobicistat and other strong CYP3A4i	3 (1.0)

[a]Number of patients is >251 owing to the time-varying nature of the covariates. [b]"Without a strong CYP3A4i" means without any CYP3A4i or with a weak/moderate CYP3A4i.
CYP3A4i, cytochrome P450 3A4 inhibitor; **SD**, standard deviation.

- The final PopPK model, comprising a two-compartment model with first order absorption, is shown in **Figure 2** with the covariate equations for revumenib and M1
  - The model suggests that for revumenib:
    - Apparent clearance (CL/F), central volume of distribution, intercompartmental clearance, and peripheral volume of distribution increase with increasing body weight
    - CL/F decreases with decreasing albumin
    - The absorption rate constant decreases when revumenib is administered with food
    - There is no absorption lag time (Tlag) with the oral solution or tablet formulations; however, a modest decrease in Tlag is observed in male and Asian patients
    - Bioavailability increases when revumenib is administered concomitantly with cobicistat or other strong CYP3A4i
  - For M1, the model suggests that:
    - Apparent metabolite clearance (CLm/F) and intercompartmental metabolite clearance increase with increasing body weight
    - CLm/F decreases when revumenib is administered concomitantly with cobicistat
    - The fraction of revumenib converted to metabolite decreases when revumenib is administered concomitantly with cobicistat or other strong CYP3A4i
- The parameter estimates for the final PopPK model are presented in **Table 2**
- Goodness-of-fit plots for the final model are shown in **Figure 3**

RESULTS

Figure 2. Final PopPK model



$$\frac{CL}{F}\,(L/hr) = 18.3 \times \left(\frac{Weight\ (kg)}{69.8}\right)^{0.287} \times \left(\frac{ALB\ (g/L)}{38}\right)^{0.977}$$

$$Vc/F\,(L) = 121 \times \left(\frac{Weight\ (kg)}{69.8}\right)^{0.716}$$

$$Vp/F\,(L) = 334 \times \left(\frac{Weight\ (kg)}{69.8}\right)^{0.936}$$

$$Q/F\,(L) = 12 \times \left(\frac{Weight\ (kg)}{69.8}\right)^{0.826}$$

F 1 = 1 × (1 + 110% if receiving strong CYP3A4i) × (1 + 155% if receiving cobicistat)

$$\frac{CLm}{F}\,(L/hr) = 6.99 \times \left(\frac{Weight\ (kg)}{69.8}\right)^{0.31} \times (1 - 73.2\%\ \text{if receiving cobicistat})$$

$$Qm/F\,(L/hr) = 12.3 \times \left(\frac{Weight\ (kg)}{69.8}\right)^{0.779}$$

Fm = 0.183 × (1 – 99.6% if receiving cobicistat) × (1 – 50.8% if receiving strong CYP3A4i)

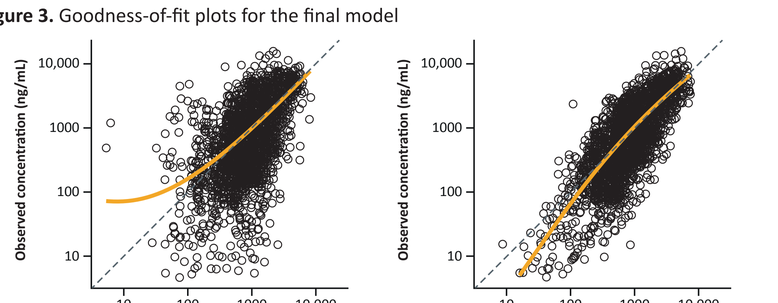
ALB, albumin; **CL(m)/F**, apparent (metabolite) clearance; **CYP3A4i**, cytochrome P450 3A4 inhibitor; **F1**, bioavailability; **Fm**, fraction of revumenib converted to metabolite; **IIV**, interindividual variability; **KA**, absorption rate constant; **Q(m)/F**, apparent intercompartmental (metabolite) clearance; **Tlag**, absorption lag time; **Vc(m)/F**, apparent (metabolite) central volume of distribution; **Vp(m)/F**, apparent (metabolite) peripheral volume of distribution.

Table 2. Final revumenib model parameter estimates

Parameters (Unit)	Estimates	%RSE	SIR %RSE	SIR 95% CI
CL/F (L/hr)	18.3	6.34	4.50	16.8–19.9
Vc/F (L)	121	6.31	5.11	110–134
Q/F (L/hr)	12.0	13.6	8.59	10.2–14.1
Vp/F (L)	334	18	11.0	274–415
KA (1/hr)	2.06	15.5	13.0	1.56–2.61
Tlag (hr)	0.227	1.04	0.512	0.225–0.229
F1	1.00	FIX		
Body weight effect on CL/F	0.287	20.8	19.0	0.178–0.395
Body weight effect on Vc/F	0.716	9.43	9.18	0.588–0.848
Body weight effect on Q/F	0.826	14.5	10.4	0.662–0.999
Body weight effect on Vp/F	0.936	25.6	20.0	0.606–1.34
Cobicistat effect on F1	1.55	12.5	10.3	1.22–1.85
Other strong CYP3A4i effect on F1	1.10	15.4	9.21	0.916–1.31
Fed effect on KA	−0.702	22.1	11.0	−0.819 to −0.517
Unknown food effect on KA	−0.511	22.3	14.2	−0.633 to −0.357
Solution effect on Tlag	−1.00	FIX		
Tablet effect on Tlag	−1.00	FIX		
Albumin effect on CL/F	0.977	24.3	20.9	0.586–1.36
Male effect on Tlag	−0.131	9.73	4.98	−0.143 to −0.117
Asian effect on Tlag	−0.144	9.2	6.97	−0.163 to −0.124
Random effects[a,b]				
IIV on CL/F (CV%)[c]	53.3	5.98	5.23	47.6–59.9
Covariance (CL/F and Vc/F)	0.107	22.8	22.3	0.0609–0.154
Correlation (CL/F and Vc/F)	0.538	-	-	-
IIV on Vc/F (CV%)[c]	41.3	16.0	13.7	27.1–52
IIV on KA (CV%)[c]	237	6.86	6.01	187–317
Residual error				
Additive error on the log scale[c,d]	0.685	2.63	1.17	0.67–0.702

[a]IIV is expressed in CV% and is calculated using $\sqrt{e^{\omega^2} - 1} \times 100$; [b]The %RSE of IIV is expressed on an approximate standard deviation scale and is calculated using $(SE/\omega^2)/2 \times 100$. The %RSE of covariance is calculated using SE/parameter estimate × 100; [c]Shrinkage for IIV on CL/F, IIV on Vc/F, IIV on KA, and additive error on the log scale was 7.89%, 33.7%, 11.8%, and 5.03%, respectively; [d]Equivalent to a proportional error on the linear scale. A typical subject is a non-Asian female with weight = 69.8 kg and albumin = 38 g/L who received capsule formulation under fasted conditions without cobicistat or other strong CYP3A4i.
%RSE, percent relative standard error; **ω2**, variance of random effect; **CI**, confidence interval; **CL/F**, apparent clearance; **CV%**, percent coefficient of variation; **CYP3A4i**, cytochrome P450 3A4 inhibitor; **F1**, bioavailability; **IIV**, interindividual variability; **KA**, absorption rate constant; **Q/F**, apparent intercompartmental clearance; **SE**, standard error; **SIR**, sampling importance resampling; **Tlag**, absorption lag time; **Vc/F**, apparent central volume of distribution; **Vp/F**, apparent peripheral volume of distribution.

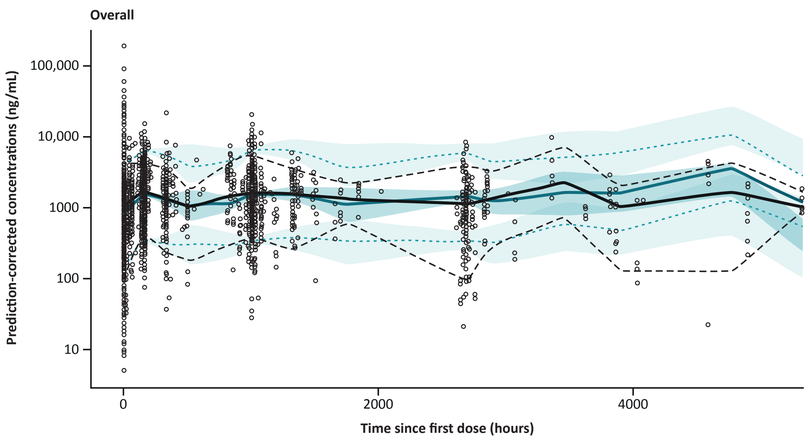
Figure 3. Goodness-of-fit plots for the final model



Dots are individual data points, solid lines are locally estimated scatterplot smoothing lines, and dashed black lines are lines of identity.

- The final PopPK model was able to predict the observed median and 5th and 95th percentiles of observed revumenib concentrations with reasonable accuracy (**Figure 4**)

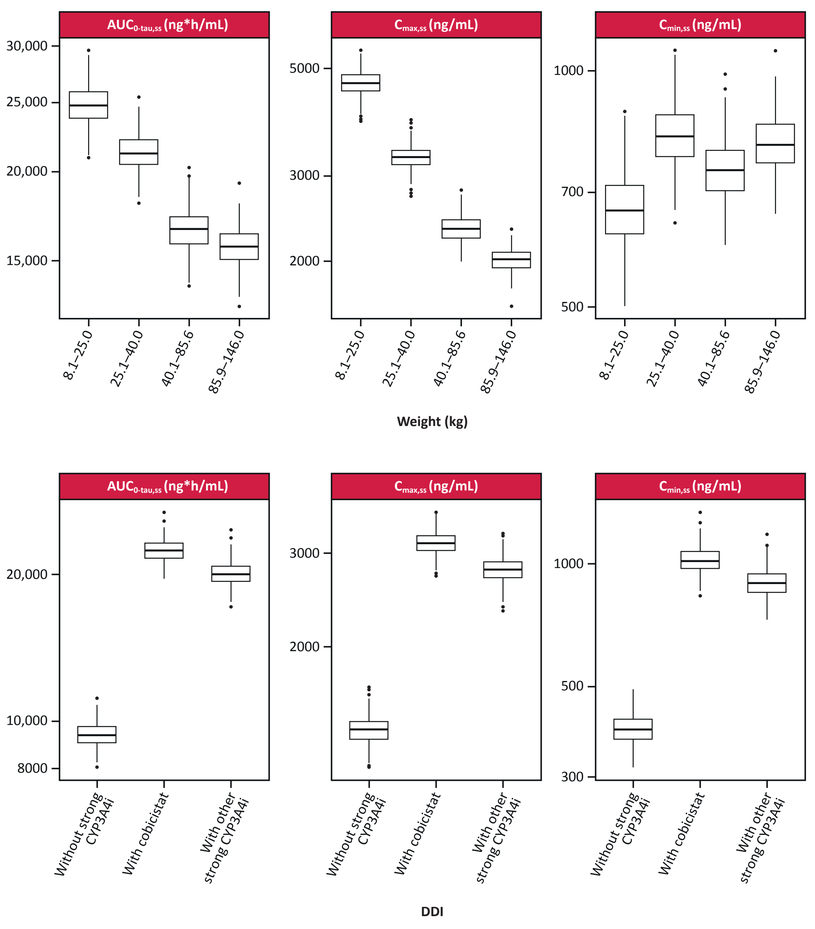
Figure 4. Prediction-corrected VPC for revumenib



Solid black lines = median of observed data; dashed black lines = P5 and P95 of observed data; dark teal shaded areas = 90% CI of the median of the simulated data; light teal shaded areas = 90% CI of the P5 and P95 of the simulated data; solid teal lines = median of the simulation data; dashed teal lines = P5 and P95 of the simulation data.
CI, confidence interval; **P5**, 5th percentile; **P95**, 95th percentile; **VPC**, visual predictive check.

- Steady-state exposure metrics were simulated and summarized by selected covariates (**Figure 5**)

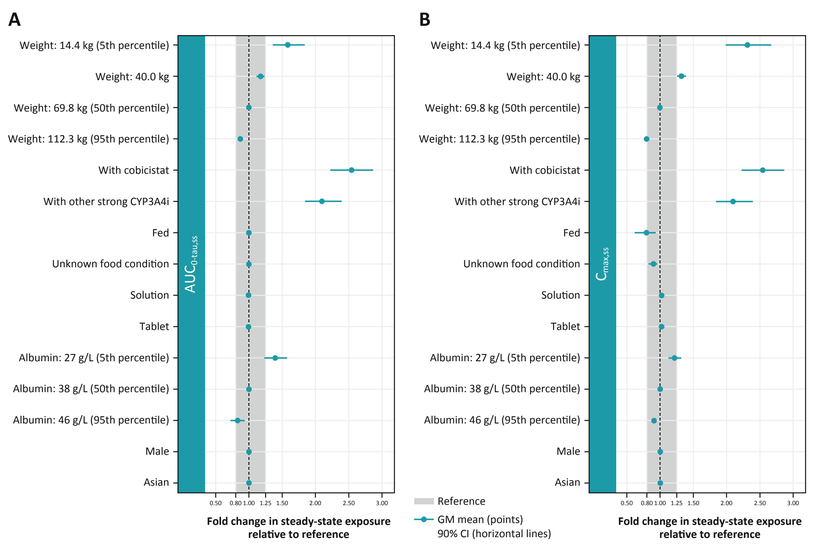
Figure 5. Box plots of covariate effects on steady-state revumenib exposure



Steady-state exposures were simulated using a nominal regimen of 163 mg every 12 hours.
$AUC_{0\text{-}tau,ss}$, area under the concentration–time curve over the dosing period; **CI**, confidence interval; **$C_{max,ss}$**, maximum concentration at steady state; **$C_{min,ss}$**, minimum concentration at steady state; **CYP3A4i**, cytochrome P450 3A4 inhibitor; **DDI**, drug-drug interaction.

- PopPK covariate analysis found no clinically meaningful effect of formulation (tablet vs. capsules vs. oral solution), food effect (low fat meal vs. fasted), sex, or race on revumenib exposure (**Figure 6**)
  - Increased exposures were observed in patients weighing <40 kg, in patients with a baseline albumin of 27 g/L, and with the concomitant use of cobicistat or other strong CYP3A4i
- PopPK exploratory analysis showed markers of hepatic function (ALT, AST, albumin, bilirubin) and renal function (i.e., serum creatinine) had no clinically significant effect on PK

Figure 6. Forest plot of covariate effects on steady-state revumenib exposure for (A) $AUC_{0\text{-}tau,ss}$ and (B) C_{max}



The gray shaded area corresponds to a ratio of between 0.8 and 1.25. The dashed vertical line corresponds to a ratio of 1 and represents the typical subject (non-Asian female with weight = 69.8 kg and albumin = 38 g/L who received capsule formulation under fasted conditions without cobicistat or other strong CYP3A4i). The values are the geometric mean and 90% CI fold change in steady-state exposure relative to the typical subject. Steady-state exposures were simulated using a dose of 163 mg every 12 hours.
$AUC_{0\text{-}tau,ss}$, area under the concentration–time curve over the dosing period; **CYP3A4i**, cytochrome P450 3A4 inhibitor; **CI**, confidence interval; **$C_{max,ss}$**, maximum concentration at steady state.

CONCLUSIONS

- The PK of revumenib was adequately described by a two-compartment model with linear elimination, first-order absorption, and an absorption lag time
- There was no clinically meaningful impact of intrinsic factors on revumenib PK, except in patients with body weight <40 kg and in patients with a baseline albumin of ≤27 g/L
- The concomitant use of strong CYP34A inhibitors increases revumenib exposures; hence, a dose reduction is proposed
- Markers of hepatic and renal function had no clinically significant effect on PK; thus, no dose adjustment is recommended for patients with mild or moderate hepatic and renal impairment
- Revumenib can be administered under fasted conditions or with a low-fat meal
- There was no impact of formulation PK (tablet vs. capsules vs. oral solution) on revumenib exposure

REFERENCE
1. Issa GC, et al. *J Clin Oncol.* 2024 Aug 9:JCO2400826. doi: 10.1200/JCO.24.00826.

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