W-016

Revumenib Physiologically Based Pharmacokinetic (PBPK) Model for Evaluation of Age Effect and CYP3A4-Mediated Drug–Drug Interaction (DDI) in Relapsed/Refractory Acute Leukemias

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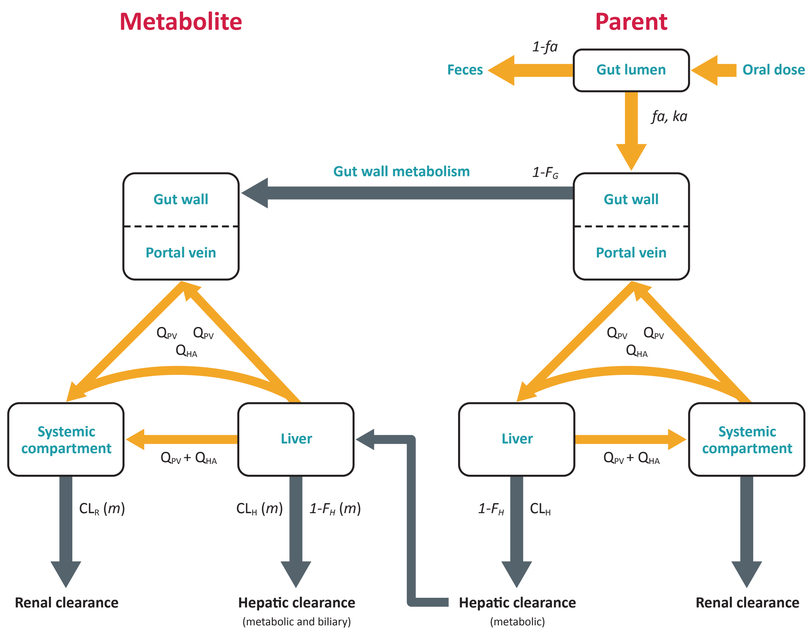
PURPOSE

- Clinical pharmacology of revumenib, a selective, oral, small-molecule inhibitor of the menin-lysine methyltransferase 2A (KMT2A) interaction that is under investigation in adult and pediatric patients with *KMT2A*-rearranged or *NPM1*-mutated relapsed/refractory acute leukemias, has been determined in clinical, modeling, and simulation studies
- Here, we report the development and application of a physiologically based pharmacokinetic (PBPK) model to assess the effects of age and co-administration with cytochrome P450 3A4 (CYP3A4) inhibitors (CYP3A4inh) or CYP3A4 inducers (CYP3A4ind) on the PK of revumenib

METHODS

- The PBPK model (**Figure 1**) was developed and verified using the Simcyp Simulator (version 22) and clinical data from adult and pediatric patients (aged 0.75 to 82 years) in the phase 1/2 AUGMENT-101 study (NCT04065399)[1]
  - Model verification involved recovery of revumenib exposure in the presence of weak (cimetidine), moderate (fluconazole), and strong (itraconazole or cobicistat) CYP3A4inh that were concomitantly administered
  - The model was in general agreement, with most revumenib-predicted exposures within twofold of observed data

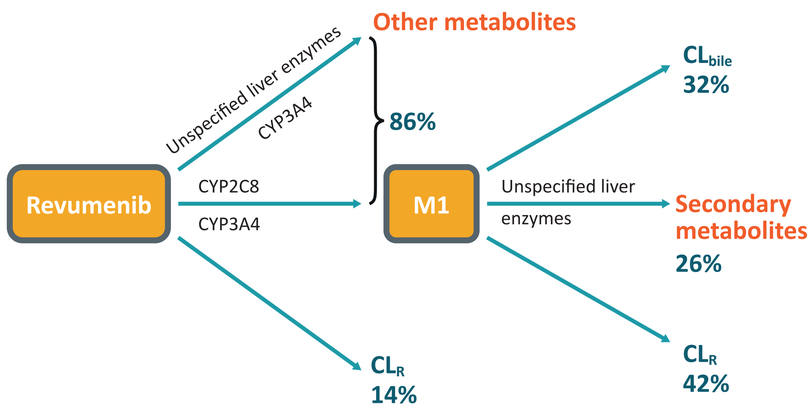
Figure 1. Minimal PBPK model with first order absorption for revumenib (parent) and M1 (metabolite)



CL_H and CL_R are hepatic and renal clearance, respectively. *fa* is the fraction absorbed from the gut, and *ka* is the associated first order absorption rate constant. F_G and F_H are the fractions escaping first pass metabolism in the gut and liver, respectively. "*(m)*" designates parameters for metabolite. Q_H, Q_{PV}, and Q_{HA} are blood flow in the liver, portal vein, and hepatic artery, respectively.
M1, metabolite; **PBPK**, physiologically based pharmacokinetic.

- The model was applied to simulate multiple doses to support dose adjustments targeting pediatric steady-state exposures equivalent to those in adults after revumenib 276 mg twice daily (BID) without a CYP3A4inh
- Doses were predicted in eight pediatric age groups using the Simcyp CYP3A4 ontogeny profile: 1 to <2 months, 2 to <4 months, 4 to <6 months, 6 months to <1 year, 1 to <2 years, 2 to <4 years, 4 to <8 years, and 8 to 16 years
- Multiple-dose adult and pediatric simulations were repeated in the presence of moderate (efavirenz) or strong (rifampicin) CYP3A4ind, and weak/moderate/strong CYP3A4inh
- A summary of revumenib and metabolite (M1) elimination processes is outlined in **Figure 2**

Figure 2. Revumenib and M1 elimination processes incorporated within the revumenib and M1 PBPK models



CL_{bile}, biliary clearance; **CL_R**, renal clearance; **CYP2C8**, cytochrome P450 2C8; **CYP3A4**, cytochrome P450 3A4; **M1**, metabolite; **PBPK**, physiologically based pharmacokinetic.

RESULTS

- The final parameters used for the simulation of revumenib kinetics are listed in **Table 1**

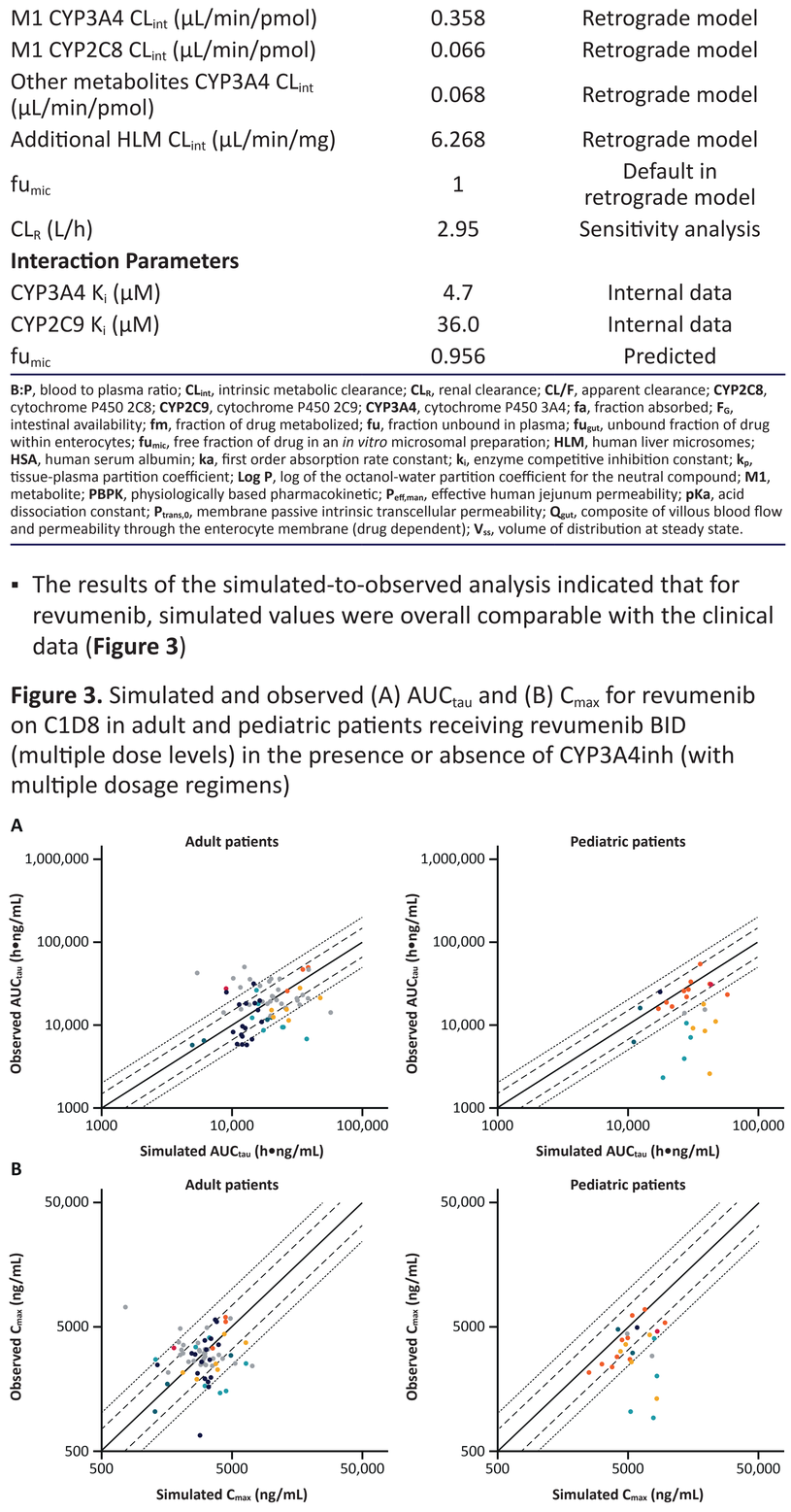
Table 1. Final input parameters for revumenib

Parameter	Value	Reference
Physicochemical and binding parameters		
Molecular weight (g/mol)	630.82	Internal data
Log P	2.94	Internal data
Compound type	Monoprotic base	Internal data
pKa	9.4	Internal data
B:P	0.70049	Predicted
Fu	0.085	Internal data
Main binding protein	HSA	Internal data
Absorption model – first order		
fu_{gut}	0.099	Internal data
$P_{trans,0}$ (x10^{-6} cm/s)	1100	Sensitivity analysis
$P_{eff,man}$ (pred) (x10^{-4} cm/s)	1.4588	Predicted
Q_{gut} (L/h)	6.0897	Estimated from retrograde model
ka (1/h)	1.0813	Predicted
fa	0.92	Internal data
F_G	0.97	Predicted
Distribution model – minimal PBPK model		
V_{SS} (L/kg)	4.1476	Predicted
K_p scalar	3	Sensitivity analysis
Elimination parameters		
CL/F (L/h)	29.07	Internal data
fm_{CYP3A4}	0.88	Internal data
fm_{CYP2C8}	0.02	Internal data
M1 CYP3A4 CL_{int} (µL/min/pmol)	0.358	Retrograde model
M1 CYP2C8 CL_{int} (µL/min/pmol)	0.066	Retrograde model
Other metabolites CYP3A4 CL_{int} (µL/min/pmol)	0.068	Retrograde model
Additional HLM CL_{int} (µL/min/mg)	6.268	Retrograde model
fu_{mic}	1	Default in retrograde model
CL_R (L/h)	2.95	Sensitivity analysis
Interaction Parameters		
CYP3A4 K_i (µM)	4.7	Internal data
CYP2C9 K_i (µM)	36.0	Internal data
fu_{mic}	0.956	Predicted

B:P, blood to plasma ratio; **CL_{int}**, intrinsic metabolic clearance; **CL_R**, renal clearance; **CL/F**, apparent clearance; **CYP2C8**, cytochrome P450 2C8; **CYP2C9**, cytochrome P450 2C9; **CYP3A4**, cytochrome P450 3A4; **fa**, fraction absorbed; **F_G**, intestinal availability; **fm**, fraction of drug metabolized; **fu**, fraction unbound in plasma; **fu_{gut}**, unbound fraction of drug within enterocytes; **fu_{mic}**, free fraction of drug in an *in vitro* microsomal preparation; **HLM**, human liver microsomes; **HSA**, human serum albumin; **ka**, first order absorption rate constant; **k_i**, enzyme competitive inhibition constant; **k_p**, tissue-plasma partition coefficient; **Log P**, log of the octanol-water partition coefficient for the neutral compound; **M1**, metabolite; **PBPK**, physiologically based pharmacokinetic; **$P_{eff,man}$**, effective human jejunum permeability; **pKa**, acid dissociation constant; **$P_{trans,0}$**, membrane passive intrinsic transcellular permeability; **Q_{gut}**, composite of villous blood flow and permeability through the enterocyte membrane (drug dependent); **V_{ss}**, volume of distribution at steady state.

- The results of the simulated-to-observed analysis indicated that for revumenib, simulated values were overall comparable with the clinical data (**Figure 3**)

Figure 3. Simulated and observed (A) AUC_{tau} and (B) C_{max} for revumenib on C1D8 in adult and pediatric patients receiving revumenib BID (multiple dose levels) in the presence or absence of CYP3A4inh (with multiple dosage regimens)



Circles represent PBPK model simulation and the corresponding observed PK parameter value; the solid line represents the unity line; dashed lines represent the area that is within 1.5-fold of the unity line, and dotted lines represent the area that is within twofold of the unity line. Control is revumenib in the absence of CYP3A4inh.
AUC_{tau}, area under the concentration-time curve over the dosing period; **BID**, twice daily; **C_{max}**, maximum concentration; **CYP3A4inh**, cytochrome P450 3A4 inhibitor; **PBPK**, physiologically based pharmacokinetic.

- The simulations also predicted comparable drug–drug interaction (DDI) liability (i.e., little age impact) in pediatric patients compared with adults during co-administration of revumenib with CYP3A4 perpetrators
  - The summary of fold change predictions in revumenib exposures in the presence of CYP3A4inh or CYP3A4ind in adult patients is shown in **Table 2**

Table 2. Prediction of fold change in revumenib exposures in the presence of CYP3A4inh or CYP3A4ind in adult patients

Perpetrator	Fold change in AUC	Fold change in C_{max}
CYP3A4inh		
Cimetidine (weak)	1.2 ↑	1.1 ↑
Fluconazole (moderate)	2.7 ↑	2.3 ↑
Itraconazole (strong)	4.1 ↑	3.3 ↑
Cobicistat (strong)	4.5 ↑	3.6 ↑
CYP3A4ind		
Efavirenz (moderate)	3.2 ↓	2.5 ↓
Rifampin (strong)	5.3 ↓	4.0 ↓

AUC, area under the concentration-time curve; **C_{max}**, maximum concentration; **CYP3A4ind/inh**, cytochrome P450 3A4 inducer/inhibitor.

- Simulations suggested similar exposure in pediatric patients (aged 6 months to 16 years) to those in adults when dosed on a mg/m^2 basis (AUC_{tau} range, 10,629–13,178 h•ng/mL) (**Table 3**)
  - A 1.6- to 2.3-fold increase in revumenib exposure was predicted in infants aged 1 to <6 months (AUC_{tau} range, 14,731–21,805 h•ng/mL)

Table 3. Simulated geometric mean plasma AUC_{tau} values for revumenib following multiple oral doses (160 mg/m^2 BID; adult equivalent dose 276 mg BID) in pediatric patients

Age range	AUC_{tau}, h•ng/mL	AUC_{tau} relative to adult mean
1 to <2 months	21,805	2.30
2 to <4 months	16,845	1.77
4 to <6 months	14,731	1.55
6 to <12 months	13,178	1.39
1 to <2 years	11,886	1.25
2 to <4 years	10,779	1.14
4 to <8 years	10,629	1.12
8–16 years	10,639	1.12

An observed geometric mean AUC_{tau} value on C1D8 in adult patients was used as the reference (AUC_{tau} = 9496 h•ng/mL).
AUC_{tau}, area under the concentration-time curve over the dosing period; **BID**, twice daily.

- The proposed starting dosage and dose modifications based on age (<6 months) and weight (body surface area [BSA]-based dosing for patients <40 kg) are shown in **Table 4**

Table 4. Modifications of selected dose

Proposed starting dose[a]	Co-administered without strong CYP3A4inh	Co-administered with strong CYP3A4inh
Patients aged ≥6 months weighing ≥40 kg	270 mg BID	160 mg BID
Patients aged ≥6 months weighing <40 kg	160 mg/m^2 BID	95 mg/m^2 BID
Patients aged 2 months to <6 months	100 mg/m^2 BID	60 mg/m^2 BID
Patients aged 1 month to <2 months	70 mg/m^2 BID	40 mg/m^2 BID

[a]Administered fasted or with a low-fat meal.
BID, twice daily; **CYP3A4inh**, cytochrome P450 3A4 inhibitor.

CONCLUSIONS

- A PBPK model was developed and verified for revumenib and M1 in adult and pediatric patients with acute leukemias
- The model was able to recover observed PK parameters for revumenib (mostly within twofold)
- Based on PBPK modeling, no dose adjustment appears necessary in pediatric patients ≥6 months old after accounting for body weight differences through BSA dosing
  - Revumenib exposure changes may require additional dose adjustment for pediatric patients aged 1 to <6 months
- Co-administration of revumenib with moderate and strong CYP3A4 inducers decreases revumenib exposures and should therefore be avoided
- In the presence of moderate or weak CYP3A4 inhibitors, no dose adjustment appears necessary; a dose reduction may be needed with a strong CYP3A4 inhibitor

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

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