Physiologically-Based Pharmacokinetic Modelling of Rivoceranib Parent and Metabolite to Project DDI Risk and Support Regulatory Decision-Making

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Aim

The PBPK model for rivoceranib, an anticancer drug acting as a tyrosine kinase inhibitor (TKI) that selectively targets vascular endothelial growth factor receptor-2, and its main pharmacologically active hydroxylated metabolite M1-1, was developed employing data from clinical studies (SAD, MAD, food effect) and validated against clinical DDI studies with itraconazole (CYP3A4 inhibitor) and rifampicin (CYP3A4 inducer). The objective of this work was to assess DDI risk for rivoceranib by utilizing PBPK modeling in lieu of clinical studies. The steps performed are depicted in the Scheme.

Methods

The mechanistic PBPK model was developed in GastroPlus® using the default Lukacova Kp method to calculate tissue distribution. Systemic clearance was parameterized using saturable metabolism via CYP3A4 and CYP2D6 enzymes. Inclusion of the metabolite M1-1 in the model supports the accurate assessment of the extent of CY3A4 (gut and hepatic) and CYP2D6 mediated metabolism. The model was developed and validated using clinical data for rivoceranib and its metabolite for doses ranging from 81-750 mg, administered with or without food. Optimization of enzyme kinetics parameters (Km and Vmax) for CYP3A4 and CYP2D6 resulted in a model that showed robust predictions for rivoceranib and metabolite exposure in both American and Chinese populations, predicting AUC_{0-t} & C_{max} within the 0.8- to 1.25-fold range of the observed values. The food effect study was conducted in the African American population, and upon accounting for population-specific race differences in CYP2D6 expression, the model adequately predicted fed conditions.

The simulated and observed PK profiles of rivoceranib and the main metabolite M1-1 at baseline following oral administration of 200 mg rivoceranib are shown in Figure (A). Percentages of rivoceranib dose dissolved; absorbed; metabolized – total; via CYP3A4 (total); via CYP3A4 in the liver; via CYP2D6 in the liver are shown in Figure (B).

Model Validation in Clinical DDI Studies

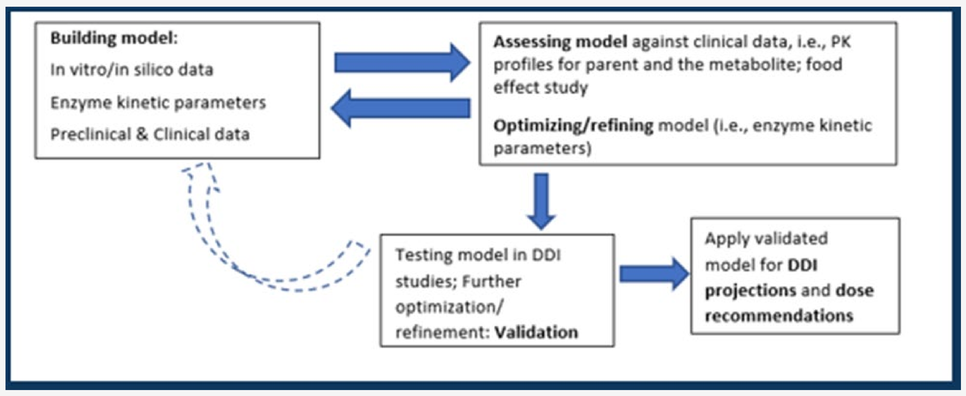
Model performance was assessed against clinical DDI studies with itraconazole and rifampicin. The simulated and observed PK profiles of rivoceranib depicted in: Figure (C) rivoceranib 200 mg alone; and Figure (D) rivoceranib 200 mg with itraconazole; Figure (E) rivoceranib 750 mg alone; and Figure (F) rivoceranib 750 mg with rifampicin. The magnitude of DDIs was projected accurately (within BE acceptance limits).

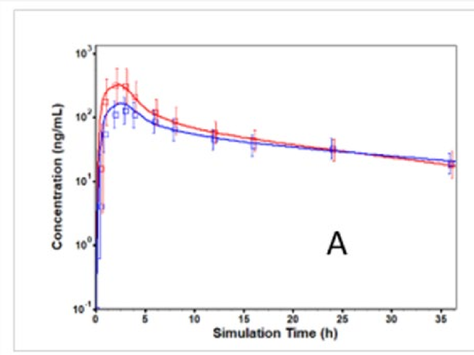
Model Application to Project DDIs

A validated PBPK model was used *in lieu* of clinical studies to assess risk of CYP3A4-mediated DDIs for an anticancer drug rivoceranib (victim) with weak/moderate CYP3A4 inhibitors (ranitidine/ fluconazole), as well as with a moderate CYP3A4 inducer (efavirenz). The results are summarized in the Table.

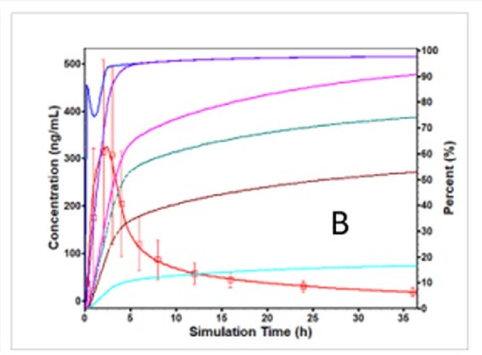
Concluding Notes

Increases in C_{max} and AUC_{0-t} by 1.2 and 1.5-fold, 1.5 and 2.3-fold, and 0.6 and 0.4-fold, with ranitidine, fluconazole, and efavirenz, respectively, were projected. Based on the PBPK simulations, a recommendation would be to avoid the use of rivoceranib for patients receiving moderate to strong CYP3A4 inhibitors/inducers.

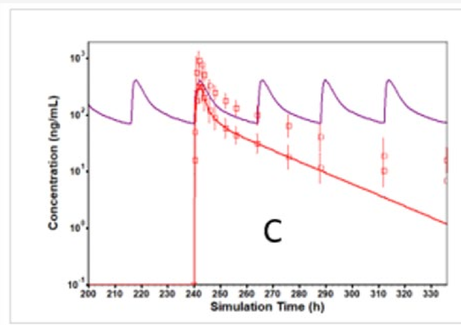




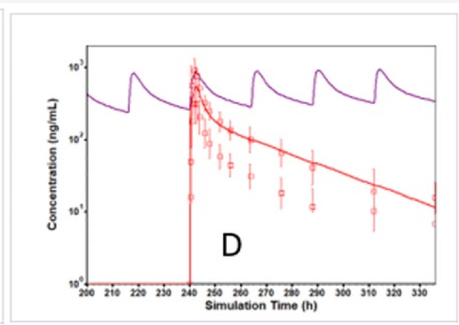
(A): Simulated (line) and observed (points) PK profiles for rivoceranib (red) and M1-1 (blue).



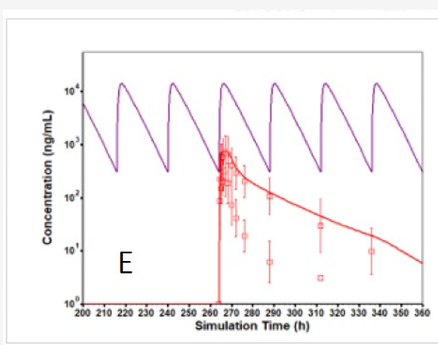
(B): Percentages of rivoceranib dose dissolved (blue); absorbed (purple); metabolized – total (pink); via CYP3A4 (green); via CYP3A4 in the liver (brown); via CYP2D6 in the liver (teal)



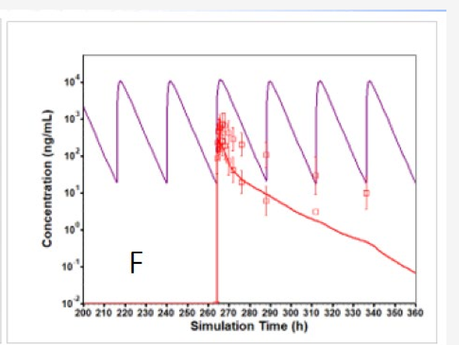
(C): Simulated (red line) and observed (mean ± SD, squares) PK profile of rivoceranib 200 mg dosed alone (i.e., without itraconazole – purple line)



(D): Simulated (red line) and observed (mean ± SD, squares) PK profile of rivoceranib 200 mg dosed with itraconazole 200 mg QD



(F): Simulated (red line) and observed (mean ± SD, squares) PK profile of rivoceranib 750 mg dosed alone (i.e., without rifampicin– purple line)



(E): Simulated (red line) and observed (mean ± SD, squares) PK profile of rivoceranib 750 mg dosed with rifampicin 600 mg QD.

Perpetrator	AUC_{0-t} Ratio	C_{max} Ratio
Ranitidine 150 mg BID	1.57	1.21
Fluconazole 200 mg QD	2.39	1.53
Efavirenz 600 mg QD	0.445	0.596

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