PHYSIOLOGICALLY BASED ABSORPTION AND PHARMACOKINETIC MODEL FOR RIVOCERANIB AND ITS MAIN METABOLITE TO ASSESS POTENTIAL CYP3A4-MEDIATED DDI RISK

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A validated PBPK model is 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), or with a moderate CYP3A4 inducer (efavirenz)

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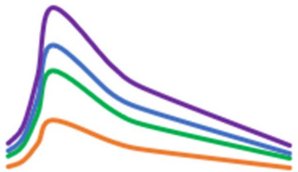
Key Findings:

Model projected increase 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

RIVOCERANIB 250 mg PK PROFILES AT BASELINE AND AFTER DDIs



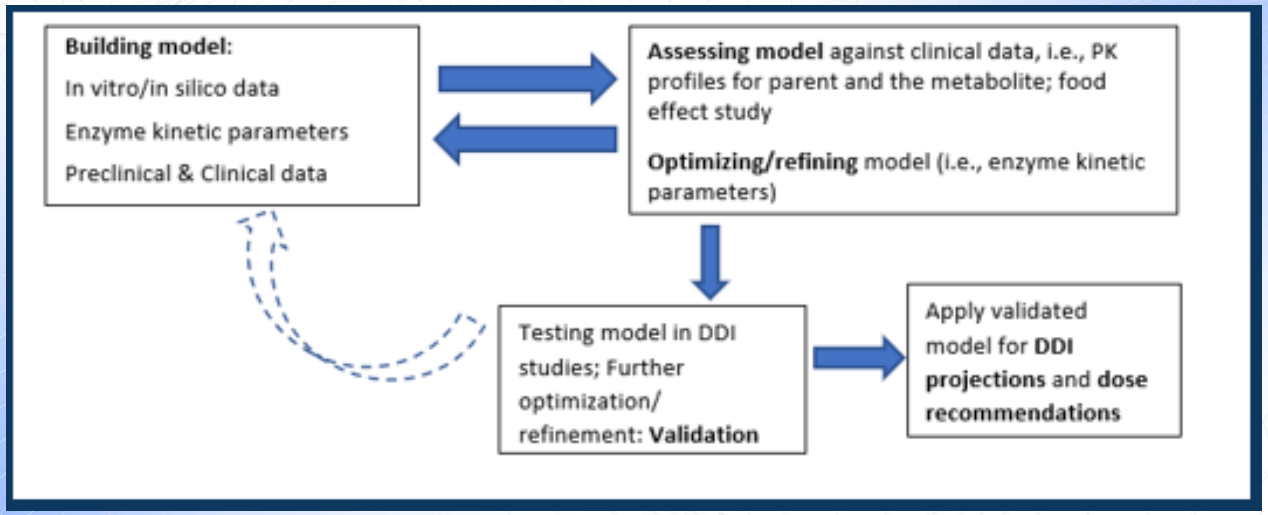
RIV-Baseline — RIV + Ranitidine

RIV + Fluconazole — RIV + Efavirenz

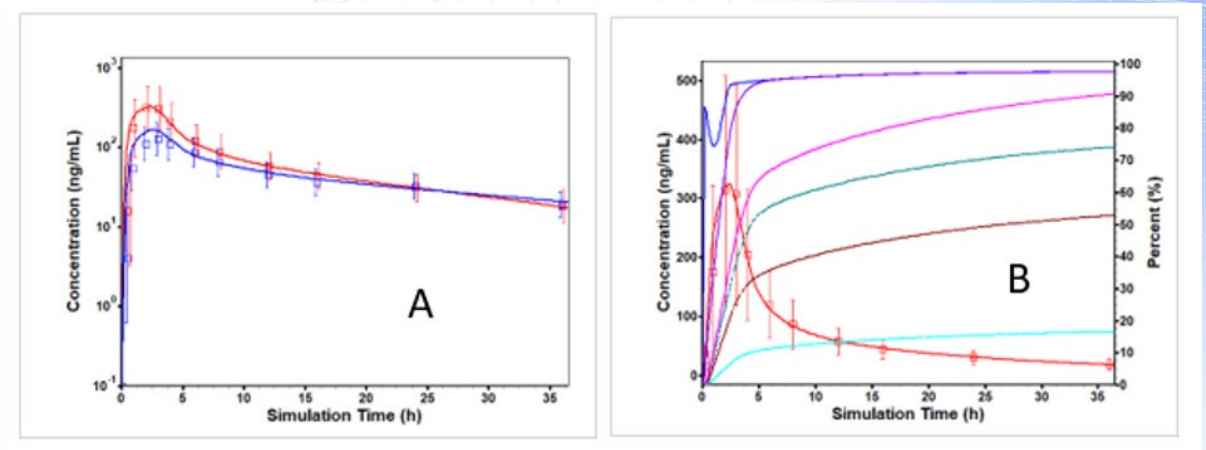
Perpetrator	AUC_{0-t} Ratio	C_{max} Ratio
Ranitidine 150 mg BID	1.57	1.21
Fluconazole 200 mg QD	2.39	1.53
Efavirenz 600 mg QD	0.445	0.596

Steps:

A PBPK model for anticancer drug rivoceranib (RIV), a tyrosine kinase inhibitor (TKI) that selectively targets vascular endothelia growth factor receptor-2 (VEGFR-2) was developed and validated to assess potential risk of CYP3A4-mediated DDIs.



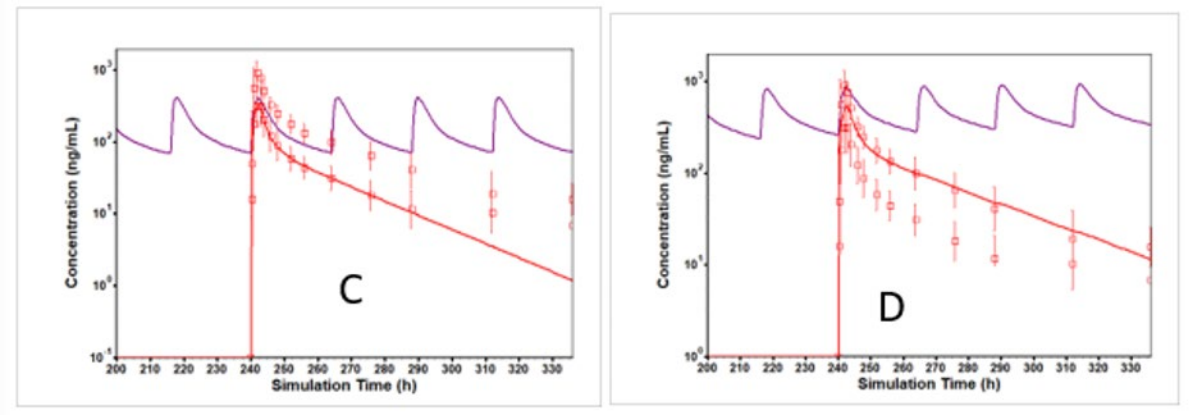
Performance of Validated Model



A. Simulated (line) versus observed (mean ± SD, squares) PK profiles of rivoceranib (red) and the main metabolite M1-1 (blue) at baseline following oral administration of 200 mg RIV.

B. Rivoceranib 200 mg oral dose: Percentages dissolved (blue); absorbed (purple); metabolized – total (pink); via CYPR3A4 (green); via CYP3A4 in the liver (brown); via CYP2D6 in the liver (teal)

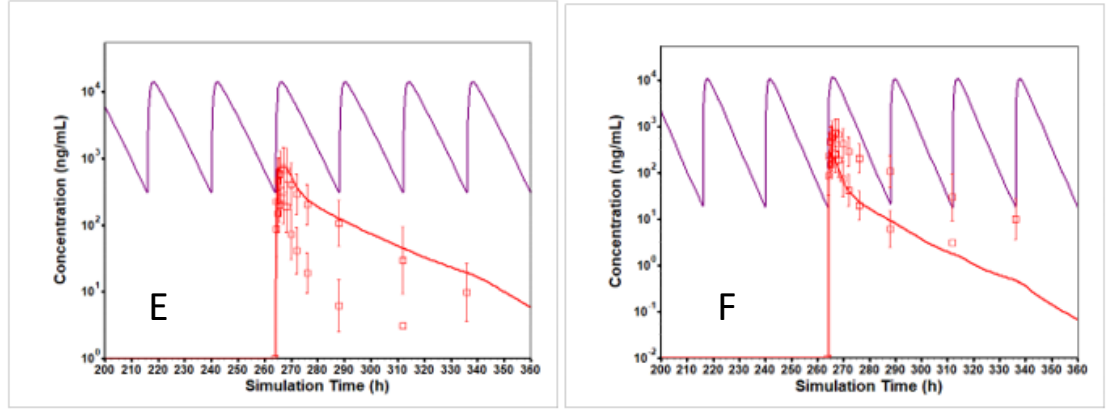
Model Verification with Clinical Itraconazole DDI Study



C. Simulated (red line) versus observed (mean ± SD, squares) PK profile of rivoceranib 200 mg oral dose at baseline (i.e., without itraconazole – purple line)

D. Simulated (red line) versus observed (mean ± SD, squares) PK profile of rivoceranib 200 mg oral dose with itraconazole oral 200 mg (purple line)

Model Verification with Clinical Rifampicin DDI Study



E. Simulated (red line) versus observed (mean ± SD, squares) PK profile of rivoceranib 750 mg oral dose at baseline (i.e., without rifampicin – purple line)

F. Simulated (red line) versus observed (mean ± SD, squares) PK profile of rivoceranib 750 mg oral dose with rifampicin oral 600 mg (purple line)

Overall Model Performance

The PBPK model accurately described:

- RIV and M1-1 exposures;
- Elimination via CYP3A4 and 2D6;
- Magnitude of itraconazole-DDIs;
- Magnitude of rifampicin-DDIs; and
- Food effect.

Predicted/observed AUC_{0-t} and C_{max} across fasted, fed, and DDI studies were within 0.8-1.25-fold range.

Estimated RIV metabolism via CYP3A4 was about 70% and <20% via 2D6.

Significance of This Work

Model projected increase 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.

This is being used as the basis to recommend RIV dose adjustment when co-administered with CYP3A4 perpetrators.