PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING OF PYROTINIB TO UNDERSTAND THE IMPACT OF INTERPLAY BETWEEN CYP3A4 AND P-GP ON ITS DDIS WITH CYP3A4 INHIBITORS/INDUCERS

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BACKGROUND

- Pyrotinib is a novel and irreversible dual pan-ErbB and tyrosine kinase inhibitor developed for treating HER2-positive advanced solid tumors.
- Pyrotinib, a BCS Class III compound, is primarily metabolized by CYP3A4, and *in vitro* results suggested that it might be a substrate for P-gp efflux transporter.

OBJECTIVE

- To develop a PBPK model for pyrotinib and qualify it with the *in vivo* data obtained after oral administrations.
- Assess the pyrotinib DDI potential when co-administered with various CYP3A4 perpetrators (i.e., inhibitors/inducers), considering the interplay between CYP3A4 and P-gp.

METHODS

- A full PBPK model for pyrotinib was developed utilizing GastroPlus®v.9.8.2. The volume of distribution was calculated using Lukacova w/lysosomal binding method.
- Tissue: plasma partition coefficients for all tissues were calculated based on *in vitro* / *in silico* (ADMET® Predictor v10.0.0.0) physicochemical properties of pyrotinib.
- Pyrotinib is metabolized by CYP3A4 and CYP2C8. A sensitivity analysis was performed with P-gp efflux transporter in the gut (Model – A) and without P-gp (Model – B).
- Simulations for pyrotinib were performed to reproduce the observed DDI effects using both pyrotinib PBPK models.
  - 80 mg of pyrotinib with co-administration of CYP3A4 inhibitors itraconazole (200 mg once daily for 14 days) and fluconazole (400 mg on day 1 and 200 mg once daily from day 2 to day 13)
  - 400 mg of pyrotinib with co-administration of CYP3A4 inducer rifampicin (600 mg once daily for 14 days) and efavirenz (600 mg once daily for 16 days)
- The built-in PBPK models for perpetrator compounds that are part of the GastroPlus DDI library were used.

METHODS

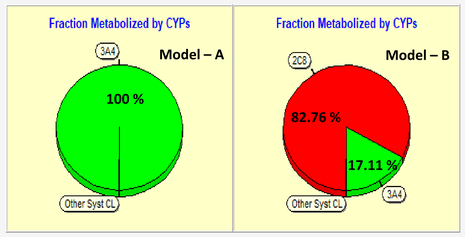
Table 1: *Key PBPK model parameters*

Properties	Parameters
logD at pH 5*	2.4
pKa	
Acid†	11.27
Base*	6.88, 4.9, 3.64, 0.72
R_{bp}*	0.74
$\%F_{up}$*	0.3
$P_{eff,\ human}$ (cm/s x 10^4)*	0.32
Precipiation time (s) ‡	15000
CYP3A4 (liver & gut) ‡	
V_{max} (mg/s/mg-enz)	2.15E-03
$K_{m,u}$ (µg/mL)	0.32
CYP2C8 (liver) – Only for Model – B ‡	
V_{max} (mg/s/mg-enz)	0.26
$K_{m,u}$ (µg/mL)	13.74
P-gp (gut) – Only for Model – A ‡	
V_{max} (mg/s)	8.75E-02
$K_{m,u}$ (µg/mL)	140

** In vitro values; † In silico values; ‡ Optimized values*

RESULTS

Figure 1: *Fraction metabolized in liver by CYP3A4 & 2C8 for model A & B.*



- The developed model with and without P-gp reproduced the observed pyrotinib plasma concentration profiles for all the doses within 0.7 - 1.3 prediction fold error.

Table 2: *Model – A prediction summary*

	Observed*		Predicted		Pred/Obs	
Dose (mg)	C_{max} (ng/mL)	AUC_t (ng-h/mL)	C_{max} (ng/mL)	AUC_t (ng-h/mL)	C_{max}	AUC_t
80	27.7	455.0	29.8	555.3	1.08	1.22
160	56.7	905.0	40.6	778.8	0.72	0.86
240	101.0	1620.0	75.5	1457.9	0.75	0.90
320	107.0	2220.0	115.4	2232.0	1.08	1.01
400	153.0	2850.0	158.9	3075.4	1.04	1.08

Table 3: *Model – B prediction summary*

	Observed*		Predicted		Pred/Obs	
Dose (mg)	C_{max} (ng/mL)	AUC_t (ng-h/mL)	C_{max} (ng/mL)	AUC_t (ng-h/mL)	C_{max}	AUC_t
80	27.7	455.0	26.4	470.3	0.95	1.03
160	56.7	905.0	55.1	982.4	0.97	1.09
240	101.0	1620.0	87.7	1542.1	0.87	0.95
320	107.0	2220.0	124.7	2162.7	1.17	0.97
400	153.0	2850.0	167.2	2855.8	1.09	1.00

** Reported mean PK parameters*

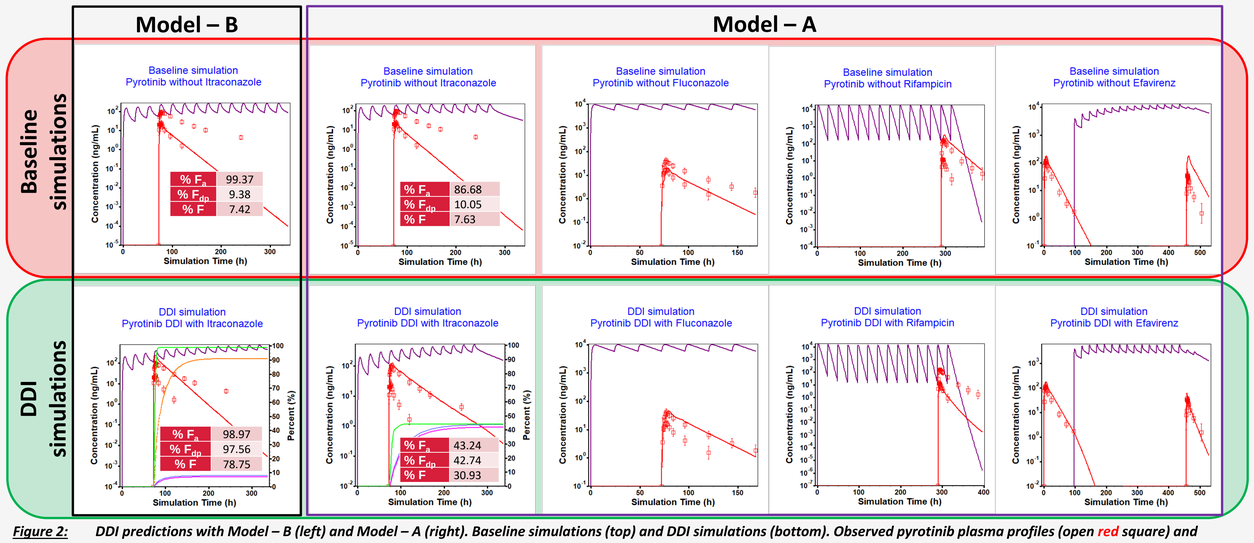


Figure 2: *DDI predictions with Model – B (left) and Model – A (right). Baseline simulations (top) and DDI simulations (bottom). Observed pyrotinib plasma profiles (open red square) and simulated plasma profile (solid red curve), fraction metabolized by CYP2C8 in liver (solid orange curve), fraction metabolized by CYP3A4 in liver (solid pink curve), total fraction metabolized by CYP3A4 in liver & gut (solid purple curve), and total fraction absorbed (solid green curve)*

Table 4: *Prediction accuracy comparison with Guest's criteria for DDI between pyrotinib, itraconazole, rifampicin, fluconazole and efavirenz*

Victim	Perpetrator	Ratio (DDI / Baseline)				Guest limits			
		Obs	Pred	Obs	Pred	Up Lim	Low Lim	Up Lim	Low Lim
		C_{max}		AUC_t		C_{max}		AUC_t	
Pyrotinib 80 mg*	ITC 200 mg	3.79	**10.17**	11.79	**9.22**	6.83	2.10	22.83	6.09
Pyrotinib 80 mg†	ITC 200 mg	3.79	**4.92**	11.79	**9.22**	6.83	2.10	22.83	6.09
Pyrotinib 400 mg†	RIF 600 mg	0.11	**0.06**	0.04	**0.03**	0.21	0.06	0.08	0.02
Pyrotinib 80 mg†	Fluco 400/200 mg	2.40	**2.25**	3.57	**2.94**	4.05	1.42	6.39	1.99
Pyrotinib 400 mg†	Efavi 600 mg	0.33	**0.29**	0.20	**0.25**	0.58	0.19	0.37	0.11

** Model without P-gp transporter; † Model with P-gp transporter; ITC: Itraconazole; RIF: Rifampicin; Fluco: Fluconazole; Efavi: Efavirenz*

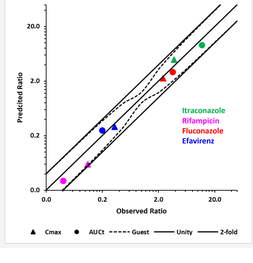


Figure 3: *Pyrotinib DDI predictions with Model – A for C_{max} and AUC*

RESULTS

- The DDI simulations by models – A and B predicted near to complete inhibition of gut metabolism, resulting in 0.5% & 1.4% fraction of drug metabolized in the gut, respectively, when co-administered with a CYP3A4 inhibitor.
- The fraction absorbed (Fa) was reduced to 43% from 87% for the model – A in the presence of CYP3A4 inhibitor due to more effective efflux by P-gp, while the Fa for model – B (no P-gp) remained unchanged (99 %).
- The model – B without P-gp efflux transporter over-predicted the observed DDI with itraconazole by 2.68-fold for C_{max}, but AUC was reasonably matched (0.97-fold).
- In case of the model with P-gp efflux, DDI prediction with itraconazole was within 0.8 – 1.3-fold for C_{max} and AUC.
- The DDI predictions with fluconazole, rifampicin, and efavirenz were within a 2-fold error and Guest limits for the model with P-gp (Table-4).

CONCLUSION

- The PBPK model for pyrotinib accounting for P-gp efflux and CYP3A4 metabolism in the gut successfully explains the interplay between P-gp and CYP3A4.
- The model – A also supports that CYP3A4 is the primary enzyme for metabolism and CYP2C8 may have no or very minor contribution.
- A P-gp efflux plays a more significant role when the gut CYP3A4 is inhibited, resulting in lower Fa, and consequently in a lower DDI effect for C_{max} than AUC.

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