

Physiologically Based Pharmacokinetic Modeling of a CYP3A4-Mediated Drug-Drug Interaction

Prediction of Victim of Induction, not Inhibition, with a Moderate Fraction Metabolized by CYP3A4

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Introduction

In vitro studies, as part of the standard clinical development program, were performed in order to define the metabolic pathway for the drug. Cryopreserved hepatocytes, microsomes (hepatic and intestinal) and recombinant CYP enzymes were used to identify metabolic pathways, characterize key metabolic entities and understand CYP induction and inhibition in rat, dog and human. The human data were used in the development of a physiologically based pharmacokinetic (PBPK) model to guide understanding of the drug-drug interaction (DDI) potential for the drug development candidate.

Objectives

To develop a PBPK model using GastroPlus® to assess the DDI liability of a new compound with 50% metabolism through CYP3A4 as victim of:

- a strong CYP3A4 inhibitor
- a strong CYP3A4 inducer

Materials and Methods

Base Model Development and Validation

All simulations were conducted using the GastroPlus® software (v 9.8; Simulations Plus Inc., Lancaster CA). The program's Advanced Compartmental Absorption and Transit (ACAT™) model was used to describe the intestinal absorption; this model was paired with the PBPKPlus™ module to describe the pharmacokinetic distribution and clearance. Descriptions of human physiologies were generated by the Population Estimates for Age-Related (PEAR) Physiology™ module. Tissue/plasma partition coefficients were calculated using the Lukacova equation assuming homogenous drug disposition into each tissues by a process of passive diffusion.

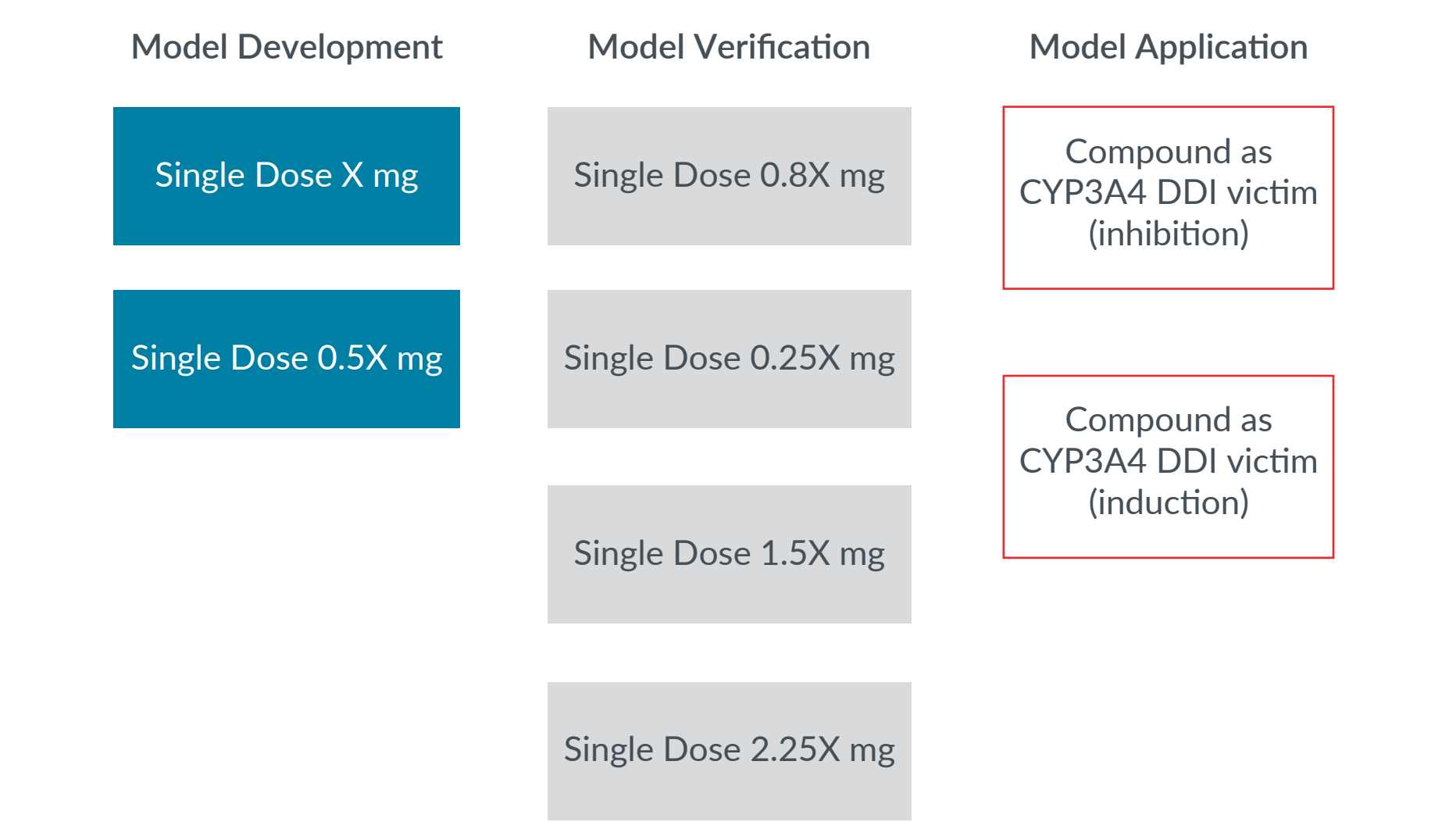
Physico-chemical properties and *in vitro* measurements for the molecule, including molecular weight, log P, pKa, solubility across various pH values, solubility in fasted state simulated intestinal fluid (FaSSIF), solubility in fed state simulated intestinal fluid (FeSSIF), permeability across MDCK cell monolayer, as well as intrinsic clearance in both microsomes and hepatocytes were used as input values to the base model. In addition, dissolution profiles were also incorporated into the model.

Metabolic clearance of the drug in liver was based on *in vitro* values for the expression of CYP3A4 in the liver, and residual clearance due to other metabolic processes were fitted to the *in vivo* data.

Pharmacokinetic data from a single dose clinical trial of the drug in the fasted state in healthy normal volunteers were used for the development and validation of PBPK model; doses in the trial ranges from 0.08 X mg – 2.25 X mg.

The ability of the model to predict the pharmacokinetic data from other doses, following single and multiple dose administration, was evaluated. Based on a review of the literature with PBPK models in GastroPlus® for CYP3A4 sensitive substrates, the model was deemed acceptable if the predicted PK parameters were within 2-fold of the observed PK parameters for the compound^[1], and model performance was assessed in terms of the fold-error between the observed and calculated PK parameters, as a ratio of Predicted Parameter/Observed Parameter (Table 1).

Figure 1. Overview of Model Development, Verification and Application



Drug – Drug Interaction Simulations – CYP3A4 Inhibition by Itraconazole and CYP3A4 Induction by Rifampicin

Drug-drug interactions were predicted using simulations within the DDI Module in GastroPlus®. PBPK models of the CYP3A4 inhibitor, itraconazole, and CYP3A4 inducer, rifampicin have previously been developed and validated within the DDI GastroPlus® environment^[2, 3]. The PBPK model was used for DDI predictions of:

- 1) Inhibitory effect of 400 mg QD itraconazole QD – Simulation Approach (n = 25) (Figure 4):
- 2) Induction effect of 600 mg QD dosing of rifampicin – Simulation Approach (n = 100) (Figure 5):

The predicted geometric mean Cmax and AUC ratios (AUCr) for the compound in absence and presence of CYP3A4 inhibitor and CYP3A4 inducer were evaluated under the following criteria^[4, 5]:

- AUCr < 2: Predicted changes in plasma exposure of the compound during coadministration with CYP3A4 inhibitors or CYP3A4 inducer are considered **Negligible/Mild**
- 2 ≤ AUCr < 5: Predicted changes in plasma exposure of the compound during coadministration with CYP3A4 inhibitors or CYP3A4 inducer are considered **Moderate**
- AUCr ≥ 5: Predicted changes in plasma exposure of the compound during coadministration with CYP3A4 inhibitors or CYP3A4 inducer are considered **Severe**

Results

Base Model:

Model Performance

- The X mg base model adequately predicts all key parameters within predefined acceptance criteria except for one parameter
- This base model also adequately predicts all key parameters across the clinical dose range (except the 0.08X mg dose)

Caveats

- The base model could be improved for the 0.08X mg dose, should this dose become of utility in the clinical development plan
- Some of the *in vitro* assays demonstrated low recovery of the molecule, yielding less confidence in the parameter

Figure 2. Base Model Simulation at Target Clinical Dose

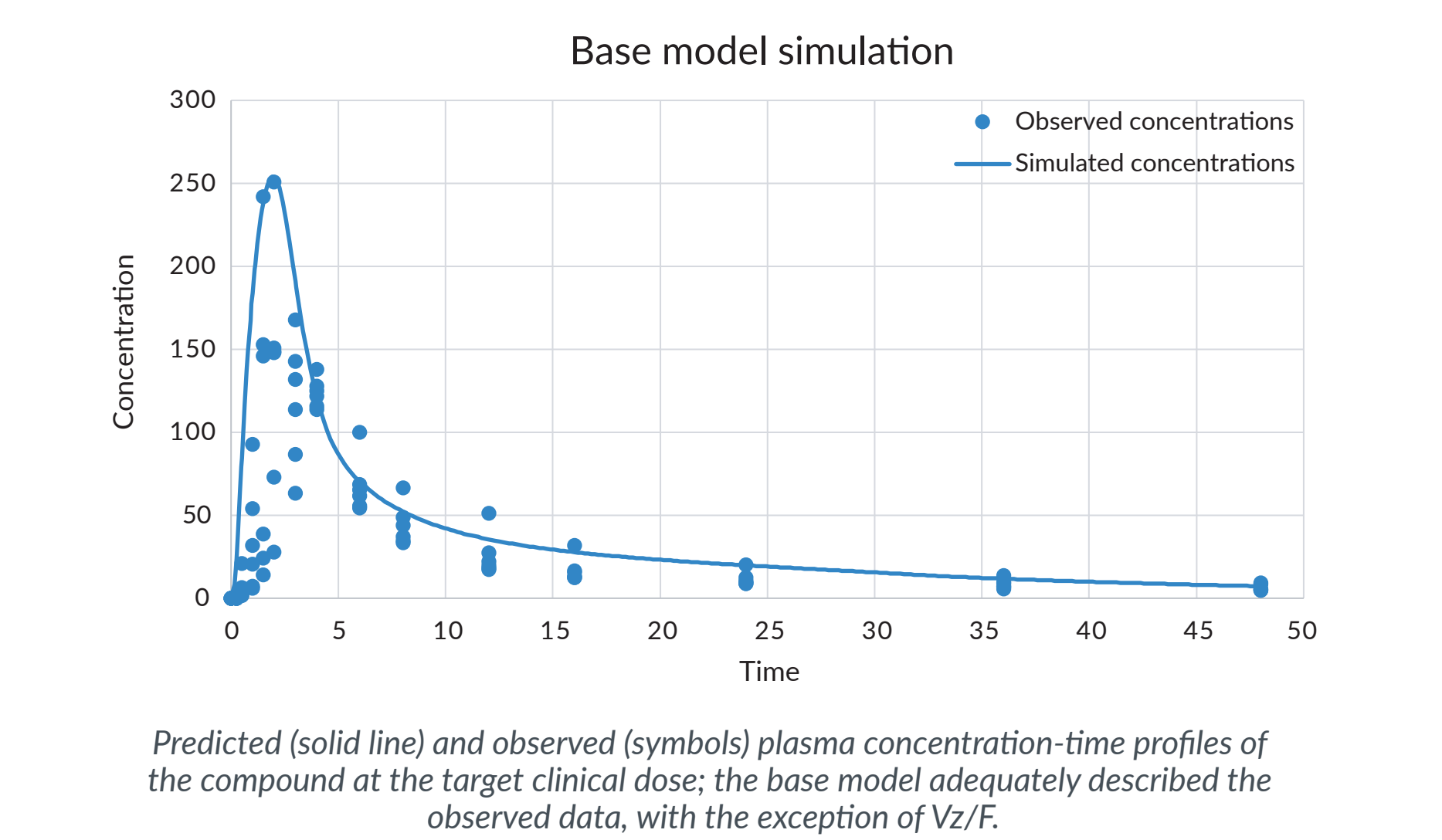
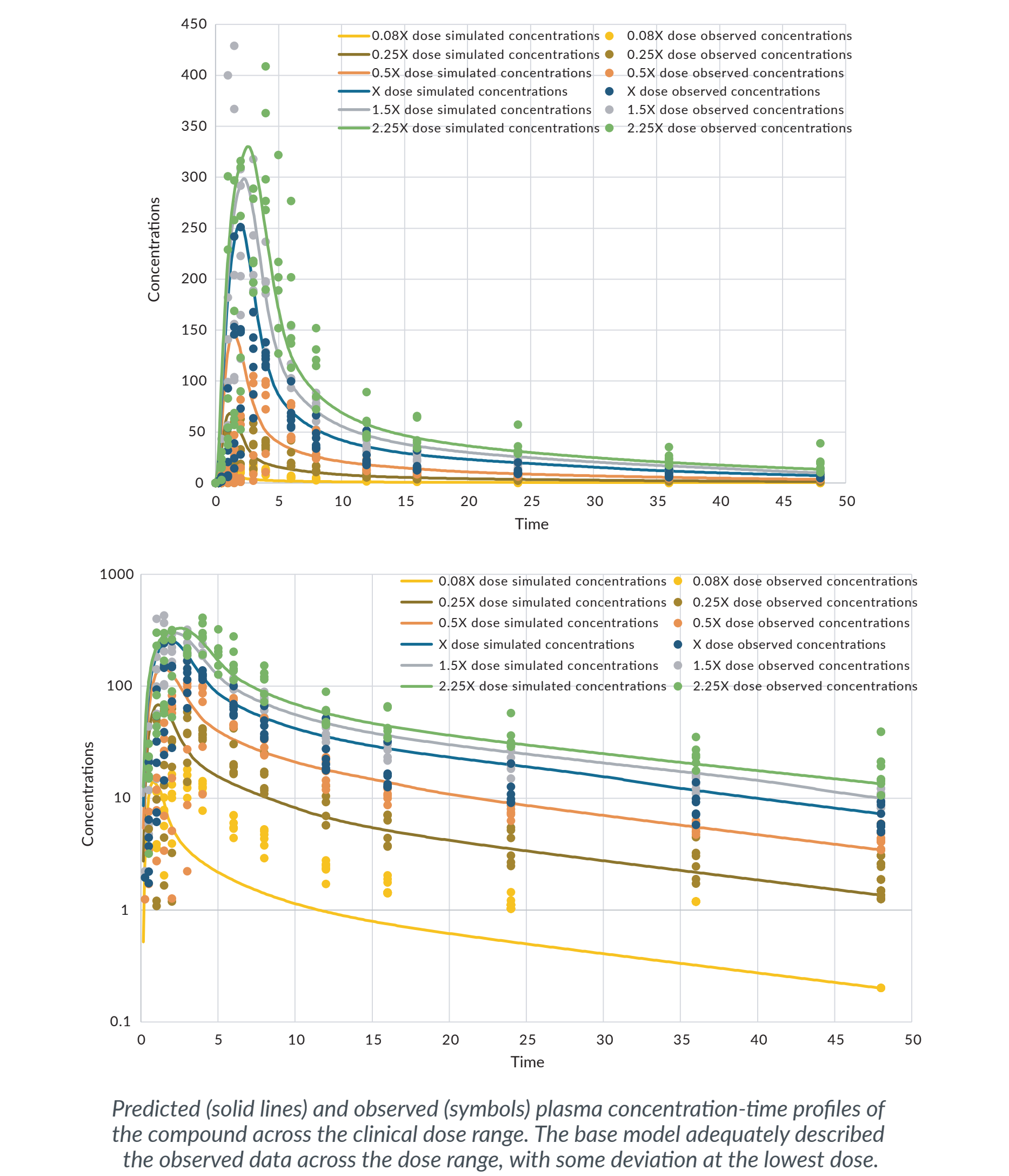


Figure 3. Base Model Simulation Across the Clinical Dose Range (linear, top panel; semi-log, bottom panel)

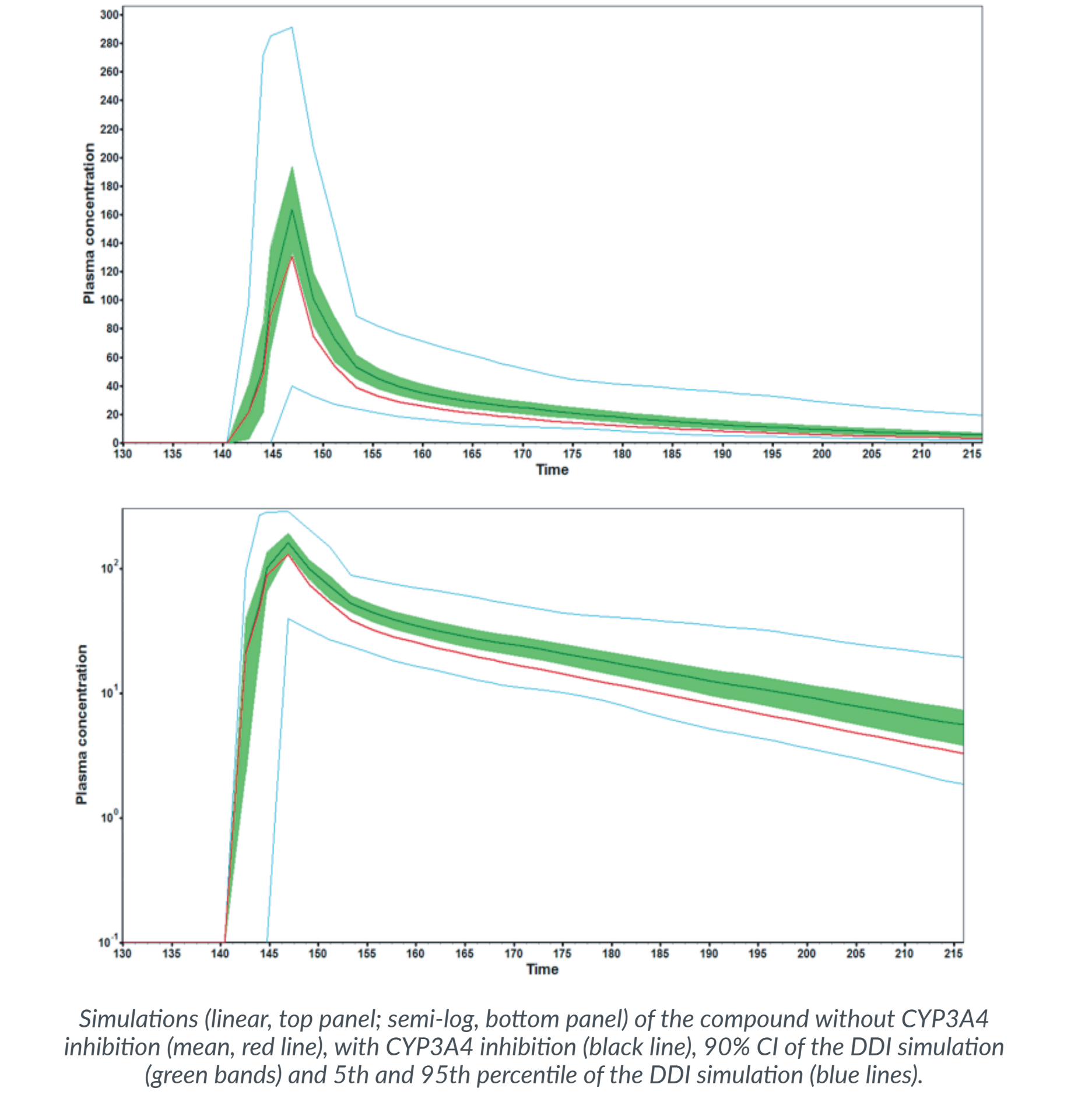


Dose	FOLD ERROR					
	Cmax	Tmax	AUClast	AUCinf	T1/2	CL/F
0.08X	0.84	0.4	0.55	0.51	1.72	1.81
0.25X	1.51	0.56	0.97	0.87	0.65	1.08
0.5X	1.73	0.48	1.13	0.97	0.61	1
X	1.62	1	1.48	1.34	0.64	1.66
1.5X	0.99	0.93	1.15	1.08	0.66	1.26
2.25X	0.99	0.9	0.99	0.87	0.74	1.11

Drug – Drug Interaction Predictions

Effect of a Strong CYP3A4 Inhibitor, Itraconazole:

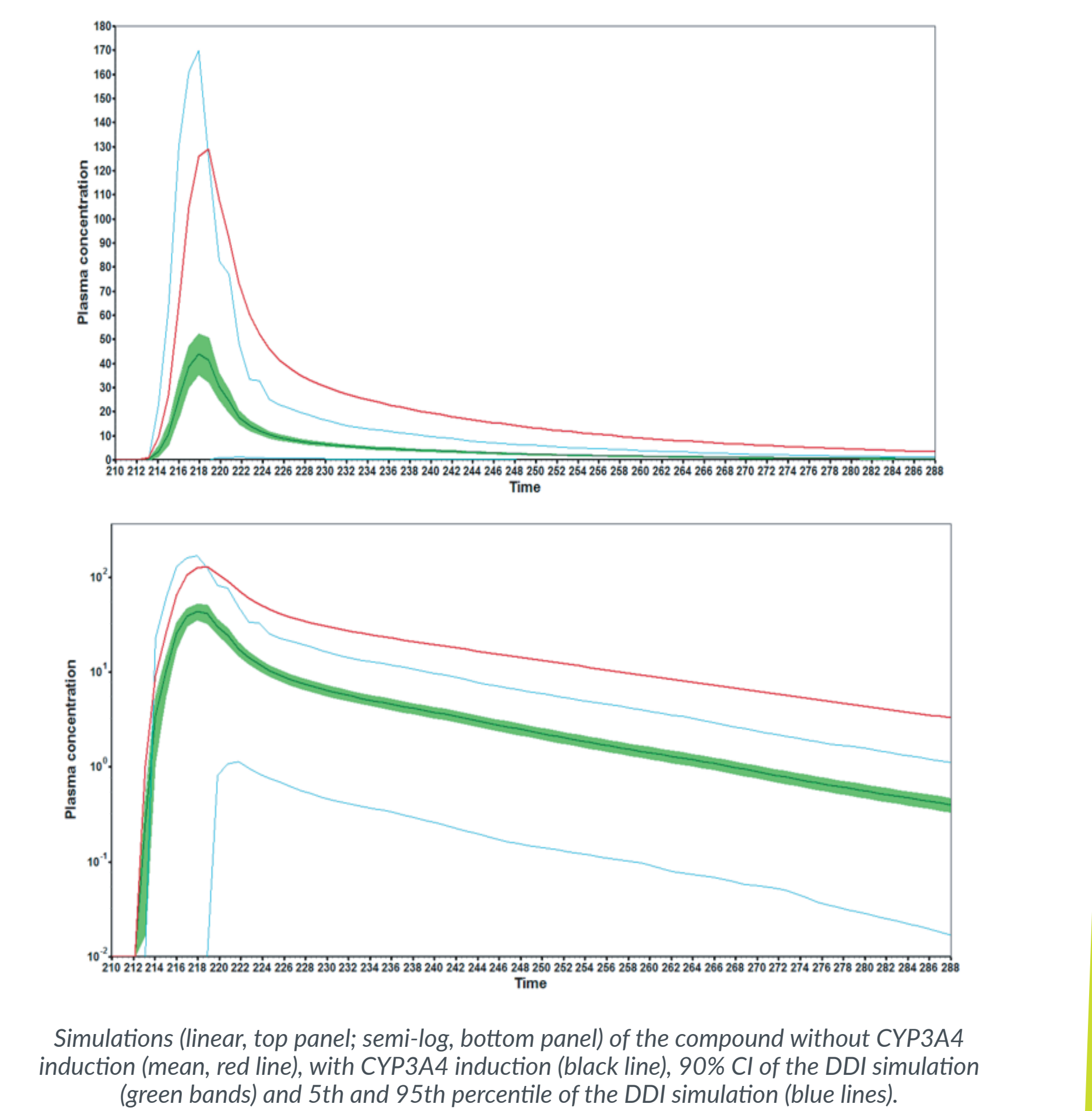
Figure 4. Effect of Strong Inhibition of CYP3A4 by Itraconazole on the Single Dose Pharmacokinetics of the Compound



Geometric mean Cmax increased by 8% and geometric mean AUC(0-t) increased 33%; the predicted changes in the plasma exposure of the compounds with coadministration of a strong CYP3A4 inhibitor are considered negligible/mild.

Effect of a Strong CYP3A4 Inducer, Rifampicin:

Figure 5. Effect of Strong Induction of CYP3A4 by Rifampicin on the Single Dose Pharmacokinetics of the Compound



Geometric mean Cmax decreased by 70% and geometric mean AUC(0-t) decreased 80%; the predicted changes in the plasma exposure of the compounds with coadministration of a strong CYP3A4 induction are considered moderate to severe.

Discussion and Impact

Guidance on allowable concomitant medications for an upcoming clinical trial was needed, with respect to the compound's predominant metabolic pathway, CYP3A4.

Based on the results of the DDI simulations, it can be suggested that no further action would be required for the inclusion of moderate or strong CYP3A4 inhibitors in upcoming clinical trials. However, a clinical study to further assess the impact of CYP3A4 induction on the pharmacokinetics of the compound; a clinical trial would be important to evaluate potential reduction in exposure and consequent possible lower efficacy.

REFERENCES

- [1] Sager JE, Yu J, Ragueneau-Majlessi I, Isoherranen N. Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation Approaches: A Systematic Review of Published Models, Applications, and Model Verification. Drug Metab Dispos. 2015 Nov;43(11):1823-37.
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