QUANTIFICATION OF THE EFFECTS OF INVESTIGATIONAL DRUGS AS VICTIMS OR PERPETRATORS OF CYP-MEDIATED DRUG INTERACTIONS INVOLVING INHIBITION IN THE SIMCYP SIMULATOR

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Document type: Briefing Book
Document status: DRAFT
Release date: DECEMBER 16, 2022
Number of pages: 88

Table of Contents

Abbreviations

ADAM	Advanced dissolution, absorption and metabolism model
ADME	Absorption, distribution, metabolism and excretion
AFE	Average fold error
AUC	Area under the plasma versus concentration time curve
C_{max}	Maximum plasma concentration
CL_{int}	Intrinsic clearance
COU	Context of use
DDI	Drug-drug interaction
ELF	Epithelial lining fluid
EM	Extensive metaboliser phenotype
EMA	European Medicines Agency
Fm	Fraction of a compounds systemic clearance occurring via a particular enzyme/mechanism
fu	Fraction unbound
FDA	Food and Drug Administration
FTIH	First time in human
GMFE	Geometric mean fold error
HLM	Human liver microsomes
IM	Intermediate metaboliser phenotype
IND	Investigational new drug
IV	Intravenous
IVIVE	*In vitro-in vivo* extrapolation
K_{deg}	Enzyme turnover in the liver
K_m	Michaelis constant
Kp	Tissue:plasma partition coefficient
PBPK	Physiologically-based pharmacokinetics
PD	Pharmacodynamics
Peff	Effective permeability
PK	Pharmacokinetics
pKa	pH where a drug exists as 50% ionized and 50% unionised forms
PM	Poor metaboliser phenotype
PO	Oral dosing (per os)
QSAR	Quantitative structure–activity relationship
SD	Standard deviation

TB	Tuberculosis
UAA	Upper airway alveoli/air
V_{ss}	Apparent volume of distribution at steady state

Tables and Figures

List of Tables

List of Figures

1. Executive Summary

Physiologically-based pharmacokinetic (PBPK) modelling is being increasingly used in drug development to inform drug labels and untested clinical drug-drug interaction (DDI) scenarios i.e. replace clinical studies. Thus, regulatory agencies are recommending more rigorous demonstration of the prediction accuracy of PBPK platforms in the area of their intended use. We describe a framework for qualification of the Simcyp Simulator® (V19 R1) with respect to competitive and mechanism-based inhibition (MBI) of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. Certara UK Ltd requests an EMA Qualification Opinion for the proposed Contexts of Use.

METHODS: The University of Washington Drug Interaction Database (DIDB) was used to identify controlled clinical DDI studies involving CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 where observed increases in plasma exposure of substrates greater than 20% (as a consequence of the DDI) were reported.

Studies were then selected to form part of the DDI qualification matrix if compound files for both substrate and inhibitor were available within the Simcyp Simulator. The DDI matrix, consisting of a range of weak, moderate, and strong inhibitors and substrates with varying fraction metabolised by specific CYP enzymes that were susceptible to different degrees of inhibition, were identified. Simulations were run with 124 clinical DDI studies involving competitive inhibition and 86 clinical DDI studies involving mechanism-based inhibition (MBI).

Using the Simcyp Simulator (V19 R1), ten trials of virtual subjects with demography matching that of the subjects recruited into each of the clinical studies were generated and the precise study designs were applied. The default values for the compound files (V19 R1) were used in simulations and are indicated in the compound file summaries (see Appendix 2).

The ratio of area-under-the-curve (AUC) in the absence and presence of inhibitor (AUC_i/AUC, where AUC_i and AUC are the $AUC_{(0-\infty)}$ values of the substrate in the presence and absence of inhibitor, respectively) is commonly used as a basis for prediction of metabolic DDIs, as is the maximum plasma concentration (C_{max}). Accordingly, the mean C_{max} and AUC ratios from the 10 simulated trials were compared against the mean AUC ratios from each *in vivo* study.

RESULTS: For competitive inhibition, the overall prediction accuracy was good with an average fold error (AFE) of 0.92 and 0.94 for changes in the maximum plasma concentration (C_{max}) and area under the plasma concentration (AUC) time profile, respectively, as a consequence of the DDI. For MBI, AFE values of 1.01 and 0.99 was determined for both C_{max} and AUC.

The prediction accuracy was generally comparable across all CYP enzymes, irrespective of the isozyme and mechanism of inhibition.

CONCLUSION: These findings provide confidence in application of the Simcyp Simulator® (V19 R1) for assessment of the DDI potential of drugs in development either as inhibitors or victim drugs of CYP-mediated interactions involving inhibition.

2. Background

Certara UK Ltd is submitting this briefing book for EMA qualification opinion on the suitability of the Simcyp Simulator, as a tool to predict the cytochrome P50 (CYP)-mediated drug-drug interaction (DDI) potential of victim and perpetrator drugs involving inhibition following oral and IV administration. Certara UK Ltd is considering this approach as a candidate for novel methodology qualification, based upon the EMA draft guideline entitled *"Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation*" (July 21, 2016; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211315.pdf) and is seeking the EMA opinion on the use of the Simcyp Simulator (V19 R1) as a tool to address the intended purpose as proposed in the context of use (COU) statements for high impact decisions, as per the draft EMA guideline document.

PBPK models make optimal use of available data by combining the complex interplay of physiological parameters with characteristics relating to the Absorption, Distribution, Metabolism and Excretion (ADME) of a specific drug to predict its pharmacokinetics (PK). PBPK modelling has been increasingly used for various applications to guide decision making in drug development on assessment of DDI liability, to design clinical studies, dose extrapolation in special populations including paediatrics, and investigation of formulation and food effects.[1] PBPK models that have demonstrated a good predictive performance, particularly in support of quantitative prediction of drug-drug interactions (DDIs), are often submitted to regulatory agencies.[2,3,4] Once reviewed and if accepted by health authorities they have been used to inform the prescription drug label for untested clinical scenarios. Global regulators have issued guidance documents or published best practice approaches for the application of PBPK in regulatory submissions.[5,6,7,8] Furthermore, regulatory agencies are recommending, or indeed requesting, more rigorous demonstration of the prediction accuracy of PBPK platforms in the area of their intended use.[9,10,11]

3. Proposed Context of Use (COU) Statements

The Simcyp Simulator (V19 R1) can be used to predict the effects of weak and moderate CYP inhibitors on the exposure of a drug when a clinical study with a strong CYP inhibitor has been conducted (and used to verify the fmCYP).

The Simcyp Simulator (V19 R1) can be used to predict the CYP-mediated inhibitory effect of a drug on the exposure of other CYP substrates when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the competitive inhibition effect *in vivo*).

The Simcyp Simulator (V19 R1) can be used to predict the CYP-mediated MBI effect of a drug on the exposure of other CYP substrates when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the MBI effect *in vivo*).

For scenarios where no clinical studies have been conducted, the Simcyp Simulator (V19 R1) can be used to predict the CYP-mediated inhibitory effect of a drug on the exposure of relevant CYP substrates (V19 files) if the predicted change in exposure of the substrate (because of competitive or MBI) falls in the range of the qualification dataset and in addition, the inhibitory potency of the drug falls in the range of the qualification dataset.

Sensitivity analyses on relevant parameters (range based on uncertainty associated with measurement) should be conducted to assess the risk of predicting a false negative.

4. Modeling Analysis Plan

The objective of this submission to the EMA is to receive qualification opinion on the suitability of the Simcyp Simulator to address the stated COU scenarios. Thus, one of the initial aims was to identify a DDI matrix that could be used for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 interactions to qualify the platform for CYP-mediated competitive inhibition and mechanism-based inhibition (MBI) via these enzymes. Such an analysis was conducted and published previously by Kilford *et al* [12]. As several compound files were in development at the time, some of the simulations were repeated and the updated analysis is described herein.

4.1 Simcyp Simulator Platform (V19 R1)

For the current analysis, all simulations were performed using the Simcyp Simulator (V19 R1). The program allows simple extrapolation of *in vitro* enzyme kinetic data in multiple organs, including liver and intestine, to predict pharmacokinetic changes *in vivo* in virtual populations.[13,14] Thus, in order to assess clearance predictions in a specific population, data are required for the population variables as well as for the *in vitro* metabolism of the test drug and its observed clearance in the population of interest. Genetic, physiological and demographic variables relevant to the prediction of DDIs are generated for each individual using correlated Monte-Carlo methods and equations derived from population databases obtained from literature sources. Default Simcyp parameter values for creating a virtual North European Caucasian population (physiological parameters including liver volume and blood flows, enzyme abundances) have been described previously.[15] With the exception of demographic data, all parameter values for the healthy volunteer (HV) population are the same as those used for the Caucasian population.

Scaling of *in vitro* data relevant to the ADME processes for integration into PBPK models is described in detail in Appendix 1 and briefly, hereafter. A minimal PBPK model, which considers both liver and intestinal metabolism, is incorporated in the Simcyp Simulator.[16] The model can also be expanded to a full PBPK model by inclusion of additional tissues such as adipose, brain, bone, heart, lung, muscle and skin.[13,14] Several absorption models are available within the Simcyp Simulator including a first-order absorption model and the advanced dissolution absorption metabolism (ADAM) model.[17] Changes in metabolic clearance due to reversible inhibition of enzyme activity, or changes in enzyme levels due to mechanism-based inactivation are handled using mechanistic dynamic models within the Simcyp Simulator. The underlying assumptions and operating differential equations relevant to prediction of DDI have been described in detail elsewhere.[16]

4.2 DDI Qualification Matrix

The process of identifying the DDI matrix is indicated in Figure 1. The University of Washington Drug Interaction Database (DIDB) was used to identify controlled clinical DDI studies involving CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5 where observed increases in plasma exposure of substrates greater than 20% (because of the DDI) were reported. Of those

identified, the DDI studies were then selected to form part of the qualification matrix if compound files for both substrate and inhibitor were available as compound files within the Simcyp Simulator (V19 R1). It should be noted that the substrates and inhibitors included as compound files within the Simcyp Simulator (V19 R1) had previously been selected for development based on the FDA and EMA recommendations for reference index substrates and inhibitors.

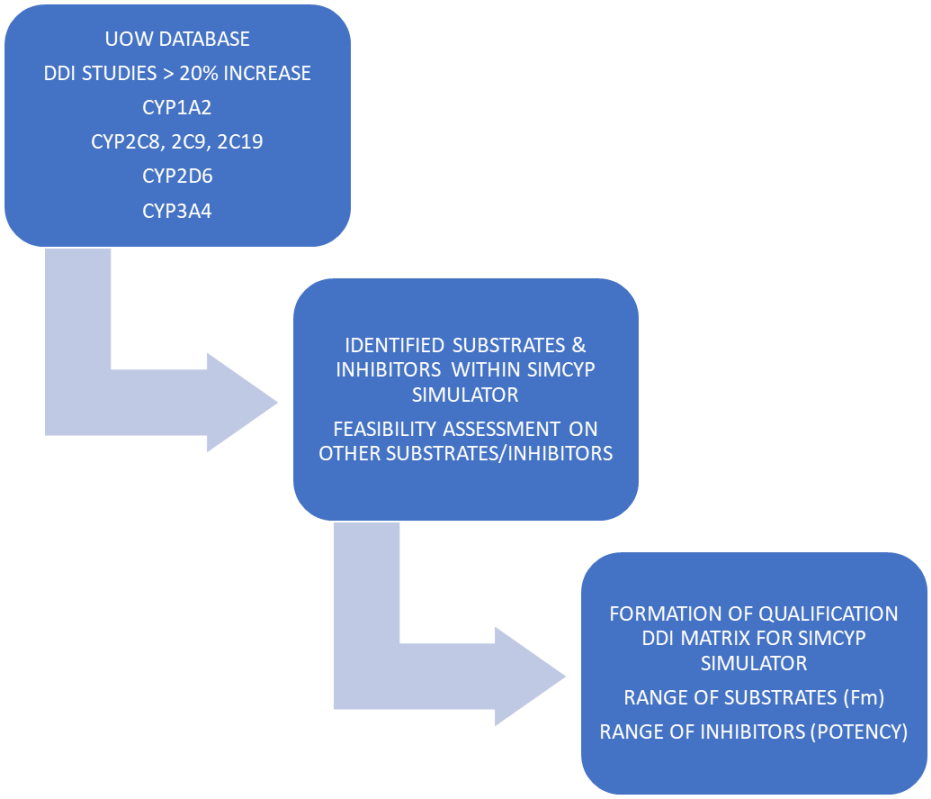


Figure 1. The workflow used to derive the DDI Qualification Matrix.

Where possible, another criterion for selection of DDI studies was to ensure the inclusion of a range of weak, moderate and strong inhibitors and substrates that were susceptible to differing degrees of inhibition. In DDI clinical studies, it is customary to use inhibitors which are known to have a strong effect. However, the inhibitory effect of a perpetrator is also dependent on the metabolic characteristics of a victim, i.e., affinity to the principal enzyme, relative contribution of a specific enzyme to overall metabolism or PK behavior of a drug, and alternative enzymatic and excretory clearance routes. Consequently, the interaction outcome of a “strong” perpetrator may be strong, moderate, or weak, depending on the victim drug. Thus, the intensity of inhibition is defined by the FDA based on the AUC change of the victim drug. Strong, moderate, and weak inhibitors give rise to an increase in AUC of a victim drug by at least 5-fold, between 2- and 5-fold, and 1.25- to 2-fold, respectively.

In addition to reference substrates and inhibitors, so-called “sensitive” substrates were also included. Usually, sensitive substrates are metabolised almost completely or to a significant extent

(>25%) by the CYP enzyme concerned, so that the inhibition by a specific inhibitor will lead to a significant increase in the exposure of the victim drug.

4.3 Development and verification of compound files within the Simulator

Prior to integration within the platform, a rigorous feasibility assessment is conducted for each compound to ensure that there are sufficient *in vitro* and clinical data available to develop and verify the files for their intended use i.e. quantitative prediction of CYP-mediated DDIs either as a victim and/or perpetrator. As part of this process, relevant information on physicochemical properties, cell permeability, protein and blood binding, *in vitro* metabolism and clinical PK is collated. Where multiple values for data are available, a meta-analysis approach is used as described in Howgate *et al.*[15] to obtain a weighted geometric mean value and variance for a particular parameter. Development and verification of each compound file is performed according to best practice approaches described in several publications and briefly below (Figure 2).

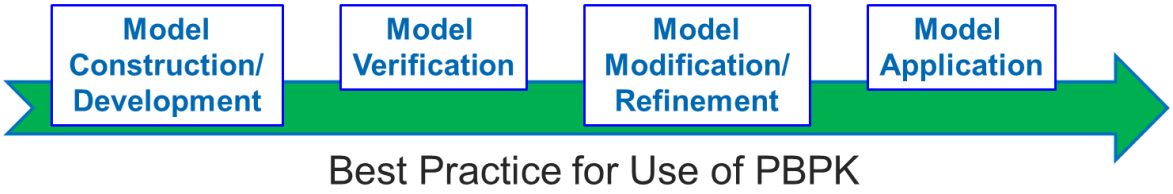


Figure 2. A typical workflow for PBPK compound file development.

Simulations using each of the compound files aims to describe concentration-time profiles from clinical datasets based on *in vitro* data alone, at least in the initial stages. Model development is performed initially using intravenous data (if available) with a focus on the distribution and elimination parameters. Thereafter, absorption related parameters are introduced into the PBPK models for each compound to predict plasma concentration-time profiles following oral administration. Of the compounds included in the qualification matrix, a first-order absorption model was applied for 31 of the 33 substrates and for 20 of the 24 inhibitors. The ADAM model was used to describe the absorption of ibrutinib, flurbiprofen, ciprofloxacin, gemfibrozil, ritonavir and verapamil.

At each stage, optimisation of relevant parameters is performed using clinical data, if necessary, to ensure accurate recovery of observed data. For a victim drug (substrate), it is important to characterise the clearance routes and demonstrate that when inhibited, the observed increase in exposures is accurately captured. For a perpetrator (inhibitor), it is necessary to ensure that after integration of the inhibitory parameters into the PBPK model, they lead to accurate prediction of clinical DDIs.

This process and the input data are captured in a compound file summary, which is version specific. The source of the input data and the clinical DDI studies for each compound, as well as the level of verification that has been performed are included in a document specific to that compound. Each

compound that has been used in the qualification dataset has a compound file summary that can be found in Appendix 2.

4.4 Simulations

To ensure that the characteristics of the virtual subjects were matched closely to those of the subjects studied *in vivo*, numbers, age range, ethnicity and sex ratios were replicated in 10 simulated trials and for the number of subjects in each clinical trial. Qualification of the DDI matrix was performed based on prediction of the observed clinical interactions for the respective drug pairings.

4.5 Data Analysis

The ratio of the area-under-the-curve of the plasma concentration-time profile (AUC) in the absence and presence of inhibitor (AUC_i/AUC, where AUC_i and AUC are the $AUC_{(0\text{-}\infty)}$ values of the substrate in the presence and absence of inhibitor, respectively) is commonly used as a basis for prediction of metabolic DDIs. In addition, the ratio of the maximum plasma concentration (C_{max}) in the presence and absence of inhibitor is also used. Accordingly, the mean C_{max} and AUC ratios from the 10 simulated trials were compared against the mean ratios from each clinical study. Equations 1 and 2 were used to calculate the average fold error (AFE) and absolute average fold error (AAFE) as described by Shimizu *et al.*[18], which were used to assess the bias and precision of the predictions, respectively.

$AFE = 10^{\frac{1}{n}\Sigma\left(log\frac{Predicted\ DDI}{Observed\ DDI}\right)}$	(Equation 1)
$AAFE = 10^{\frac{1}{n}\Sigma\left\|log\frac{Predicted\ DDI}{Observed\ DDI}\right\|}$	(Equation 2)

The data were analysed according to type of inhibition (competitive *versus* MBI) and also according to the CYP enzyme.

Predictions were assessed as to whether they fell within 1.5-fold of observed data. In addition, as some of the clinical DDIs resulted in weak to moderate interactions, the validation criteria proposed by Guest *et al.*[19] were also indicated on the graphs.

5. Results

5.1 DDI Qualification Matrix

In total, 33 substrates and 24 inhibitors were identified for inclusion in the DDI matrix for qualification of CYP-mediated inhibition using the Simcyp Simulator (V19R1) (Figure 3). There were 1234 clinical studies involving competitive inhibition and 86 clinical studies involving time-dependent inhibition (MBI).

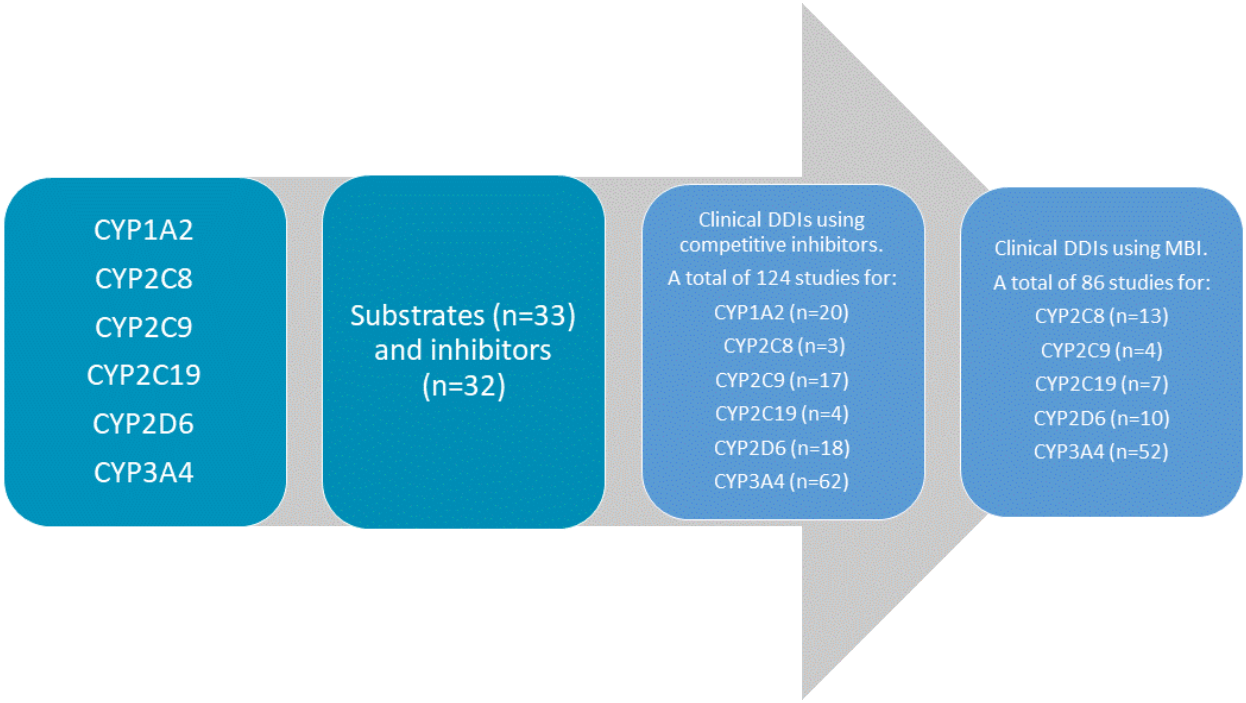


Figure 3. An overview of the DDI qualification matrix

5.1.1 Substrates

The 33 substrates identified for inclusion in the DDI matrix are shown in

Table **1**. The verification of the contributions of the CYP enzymes to each substrate is indicated in each compound file summary (Appendix 2.).

For CYP1A2, caffeine, theophylline and tizanidine were available with fraction metabolised (fm) values ranging from 75.8 to 97.9%.

Three substrates were included to evaluate CYP2C19 with $fm_{CYP2C19}$ values ranging from 38.3 to 85.8% for imipramine and S-mephenytoin, respectively.

Repaglinide (66.1%), rosiglitazone (56.1%) and amiodarone (32.2%) were included as substrates of CYP2C8.

Five CYP2C9 substrates were included, with fm_{CYP2C9} ranging from 73.1 to 98.4% for phenytoin and S-warfarin, respectively.

Six substrates were evaluated for CYP2D6-mediated DDIs with fm_{CYP2D6} ranging from 73.9 to 87.7%.

Not surprisingly, the largest range of fm values was observed for the substrates that were used to evaluate CYP3A4/5-mediated DDIs with fm_{CYP3A4} ranging from 33.7% for repaglinide up to 99.8% for nifedipine.

Across all substrates, the predicted bioavailability (F) ranged from 0.04 to 0.92 for simvastatin and rosiglitazone, respectively. Simvastatin had the lowest predicted fraction escaping first-pass

metabolism in the gut (Fg) at 0.12 and this increased up to a maximum value of 1 for a number of substrates including caffeine, theophylline, tizanidine, rosiglitazone, alprazolam and phenytoin. Gertz *et al* [18] reported observed values of 0.6, 0.9, 0.51, 0.74, 0.9, 0.21, 0.89, 0.54, 0.14, 0.75 and 0.79 for alfentanil, alprazolam, midazolam, nifedipine, quinidine, rifabutin, repaglinide, sildenafil, simvastatin, triazolam and zolpidem, respectively. With the exception of rifabutin, which was within 1.5-fold of the observed value, all other predicted Fg values were within 1.25-fold.

Table 1. Mean fraction metabolised (fm), fraction escaping gut metabolism (Fg) and bioavailability (F) for each substrate according to the enzyme of interest as calculated in the Simcyp Simulator V19 (R1).

Enzyme	Substrate	fm%	Fg	F
CYP1A2	Caffeine	97.9	1	0.81
	Theophylline	75.8	1	0.83
	Tizanidine	96.6	1	0.16
CYP2C19	S-Mephenytoin	85.8	0.89	0.34
	Omeprazole	77.9	0.96	0.5
	Imipramine*	38.31	1	0.38
CYP2C8	Amiodarone	32.2	0.73	0.38
	Repaglinide	66.1	0.92	0.76
	Rosiglitazone	56.1	1	0.93
CYP2C9	Celecoxib	83.5	0.77	0.51
	Flurbiprofen	81.9	0.96	0.92
	Phenytoin	73.1	1	0.79
	S-Warfarin	98.4	0.99	0.86
	Tolbutamide	96.8	0.99	0.84
CYP2D6	Atomoxetine	78.6	0.91	0.61
	Desipramine	81.8	0.95	0.44
	Dextromethorphan	87.7	0.9	0.21
	Metoprolol	73.9	0.97	0.45
	Nebivolol	85.7	0.92	0.17
	Tolterodine	82.7	0.99	0.29
CYP3A4/5	Alfentanil	91.8	0.54	0.34
	Alprazolam	71	1	0.83
	Amiodarone	47.1	0.73	0.38
	Aprepitant	85.2	0.6	0.48
	Atazanavir	80.2	0.94	0.36
	Clarithromycin	73.6	0.85	0.51
	Dexamethasone	86.1	0.99	0.76
	Ibrutinib	95	0.4	0.04
	Midazolam	96.2	0.6	0.29
	Nifedipine	99.8	0.67	0.42
	Quinidine	71.7	0.95	0.66
	Rifabutin	66	0.14	0.11
	Repaglinide	33.7	0.92	0.76

Sildenafil	86	0.67	0.38
Simvastatin	88.7	0.12	0.04
Triazolam	97.1	0.74	0.51
Zolpidem	48.2	0.95	0.79

* For Imipramine the V20 setting was used in V19

Simulation of 10 subjects in 10 trials each for the Sim-Healthy Volunteer population as a single dose for 96h using V19.0.96.0 (V19 Release 1).

5.1.2 Inhibitors

Across all CYP enzymes there were 24 inhibitors available for qualification of the platform (Appendix 3.); some had inhibition parameters for multiple CYP enzymes. A range of Ki values from different *in vitro* sources were available for each of the inhibitors included in this analysis and were determined using pooled human liver microsomes (HLM) or recombinant systems (supersomes, baculosomes, or bactosomes). After correction for nonspecific microsomal binding at the relevant protein concentration, an average Ki value was determined for each of the inhibitors.

Out of the inhibitors and metabolites included in the analysis, 63% had interaction parameters based on *in vitro* data and the remainder were optimised based on clinical data.

The full spectrum of strong, moderate and weak inhibitors was only available for CYP2D6 and CYP3A4.

5.2 Analysis - Competitive and Mechanism Based Inhibition Level

The results of all the individual simulations (n=210) are shown in Appendix 4.

Predicted *versus* observed changes in AUC and C_{max} across all the CYP enzymes investigated are shown in Figure 4 for competitive inhibition (n=124 DDIs) and in Figure 5 for mechanism-based inhibition (n=86 DDIs).

The prediction accuracy for the DDIs involving 23 competitive inhibitors and 18 mechanism-based inhibitors is shown in Table 2 and Table 3, respectively.

Figures relating to prediction accuracy at a inhibition mechanism/CYP enzyme/substrate level are presented in Appendix 5.[12]

Table 2. Prediction accuracy for competitive inhibition

Competitive inhibition	V19R1	
	Cmax Ratio	**AUC Ratio**
AFE (bias)	0.92	0.94
AAFE (precision)	1.20	1.20
Number Studies	98	124

Number Studies	98	124

Table 3. Prediction accuracy for MBI

MBI	V19R1	
	Cmax Ratio	**AUC Ratio**
AFE (bias)	1.01	0.99
AAFE (precision)	1.20	1.29
Number Studies	70	86
Number Studies	70	86

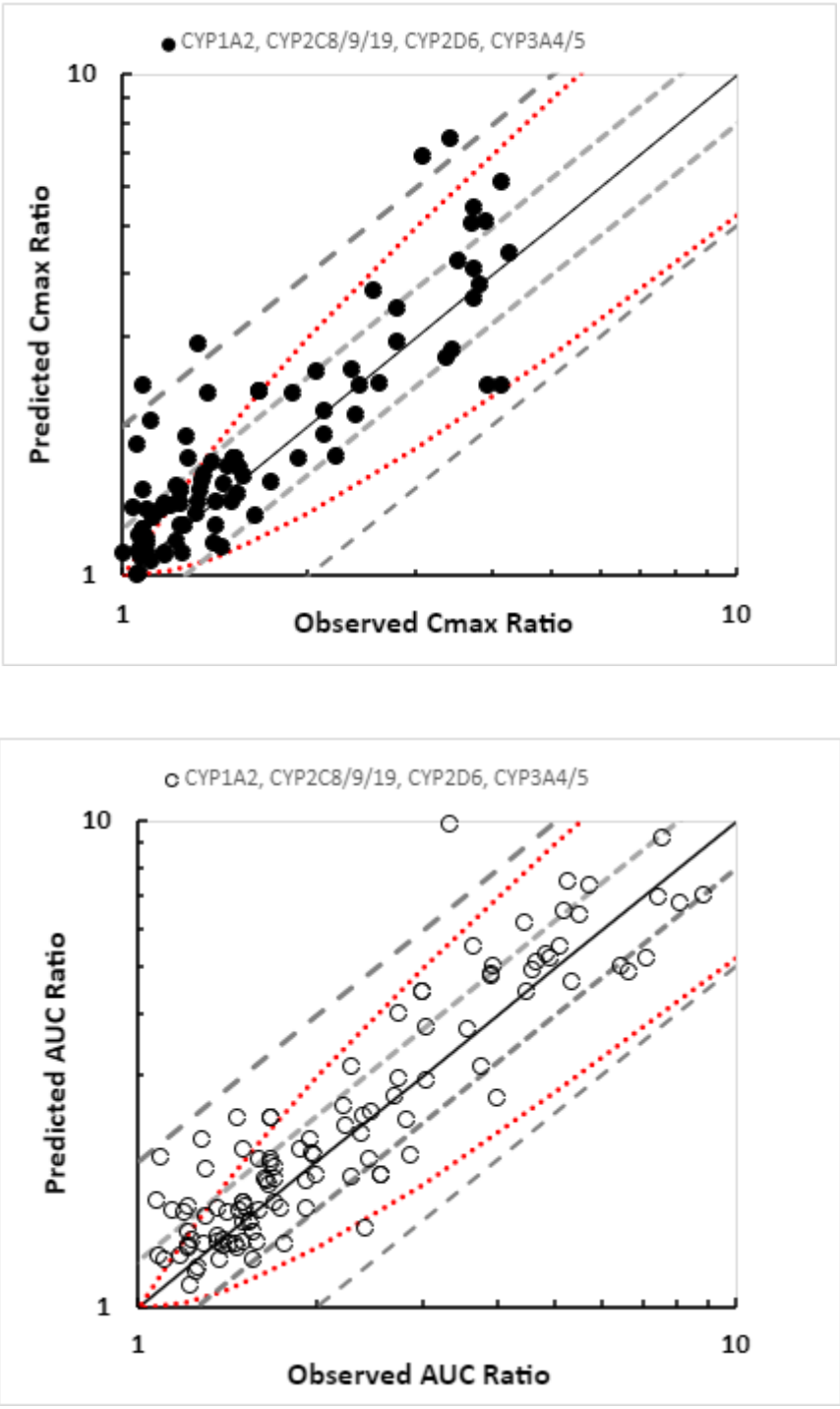


Figure 4. Predicted *versus* observed DDIs involving competitive inhibition

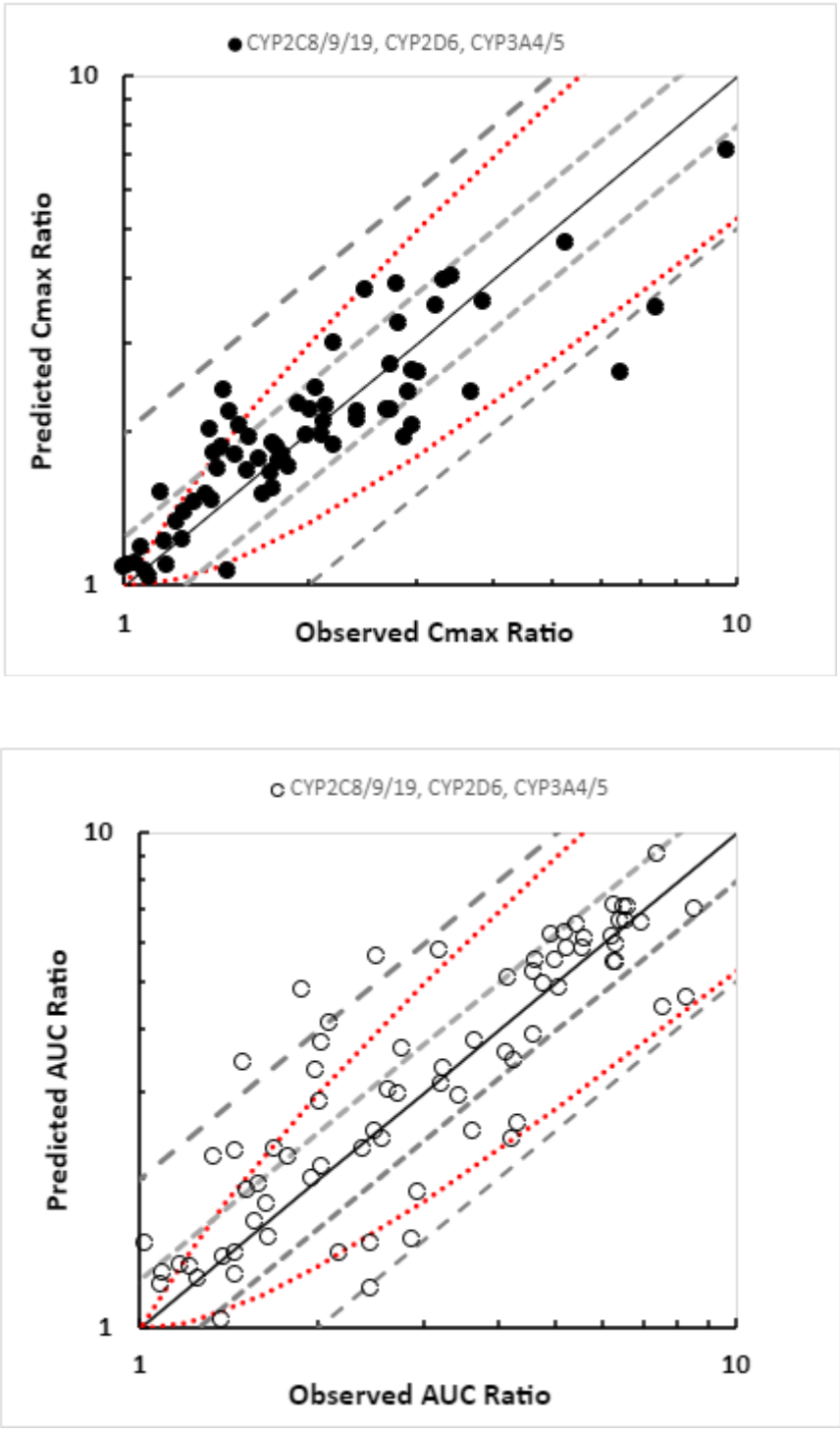


Figure 5. Predicted *versus* observed DDIs involving mechanism-based inhibition

5.2.1 Analysis – Individual CYP-Enzyme

For each enzyme, the prediction accuracy of the DDIs was evaluated against the clinical data and this is shown in Figure 6 (CYP1A2), Figure 7 (CYP2C8), Figure 8 (CYP2C9), Figure 9 (CYP2C19), Figure 10 (CYP2D6) and Figure 11 (CYP3A4/5). The prediction accuracy was generally comparable across all the CYP enzymes in the qualification DDI matrix.

For CYP1A2, the prediction accuracy was good with an AFE (bias) of 0.91 and 1.03 and an AAFE (precision) of 1.21 and 1.21 for C_{max} and AUC, respectively. Out of the 20 DDIs studied, only 3 fell outside the 1.5-fold prediction accuracy from observed AUC ratio data and 1 against the C_{max} ratio data. The clinical studies involved interactions between caffeine and fluvoxamine (1 instance), theophylline and fluvoxamine (2 studies) and tizanidine and ciprofloxacin (1 study).

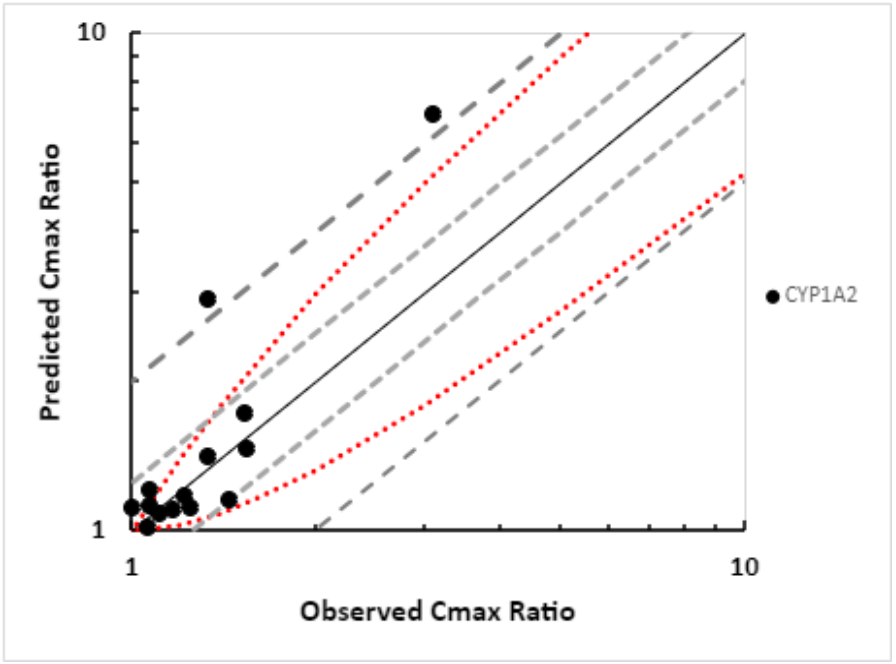
For CYP2C8 (n=16 studies), with the exception of 4 studies involving gemfibrozil, all the predictions fell within 1.5-fold of the observed clinical values for both C_{max} and AUC. In 2 of the studies, lower than normal doses of 100 mg gemfibrozil (600 mg BID typically used) were used. In the other 2 studies, it should be noted that complex study designs including a dose stagger of 12 hours was applied to assess the duration of mechanism-based inhibition. Overall, the prediction accuracy was good with an AFE of 1.08 and 0.81 and an AAFE of 1.19 and 1.28 for C_{max} and AUC, respectively.

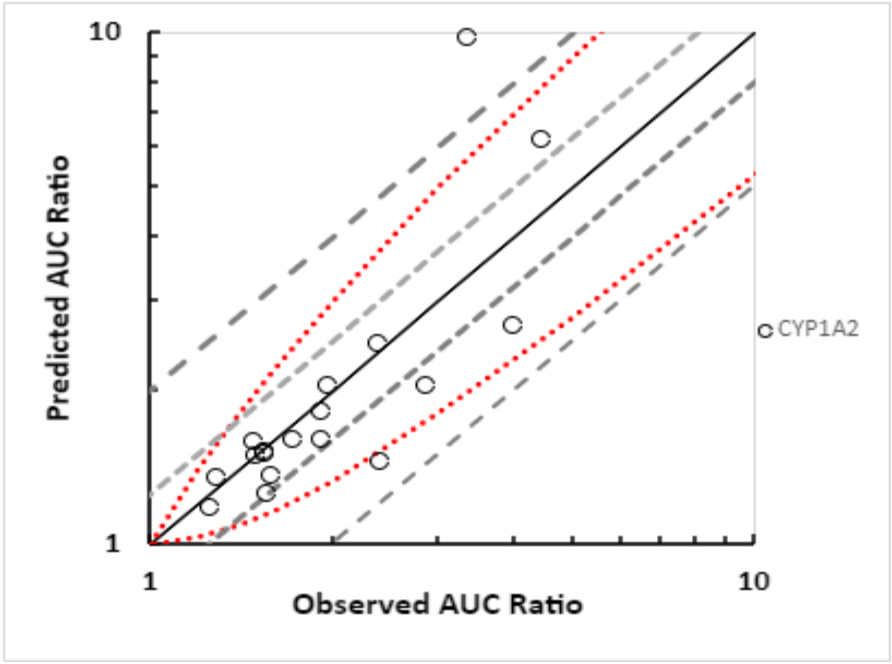
For CYP2C9 (n=21), all the predictions fell within 1.5-fold of the observed clinical values for both C_{max} and AUC. Overall, the prediction accuracy was good with an AFE of 0.89 and 1.03 and an AAFE of 1.13 and 1.15 for C_{max} and AUC, respectively.

There were 11 DDI studies available to evaluate the prediction of CYP2C19 DDIs with 3 substrates, S-mephenytoin, omeprazole and imipramine. The C_{max} was predicted with an AFE of 0.89 and AAFE of 1.13 and apart from 1, all studies fell within 1.5-fold of the observed clinical data. There was also a good prediction of the AUC ratio across the substrate studies with a bias of 1.03 and precision of 1.15.

CYP2D6 predictions were assessed for 28 clinical studies involving the 6 substrates; there was a good prediction accuracy with an AFE of 0.89 and 1.03 and an AAFE of 1.13 and 1.15 for C_{max} and AUC ratios, respectively. Three of the predictions fell outside of 1.5-fold of the observed C_{max} ratios for the substrates nebivolol and tolterodine. Two of the predictions fell outside of 1.5-fold for the AUC ratios for the substrates dextromethorphan and metoprolol.

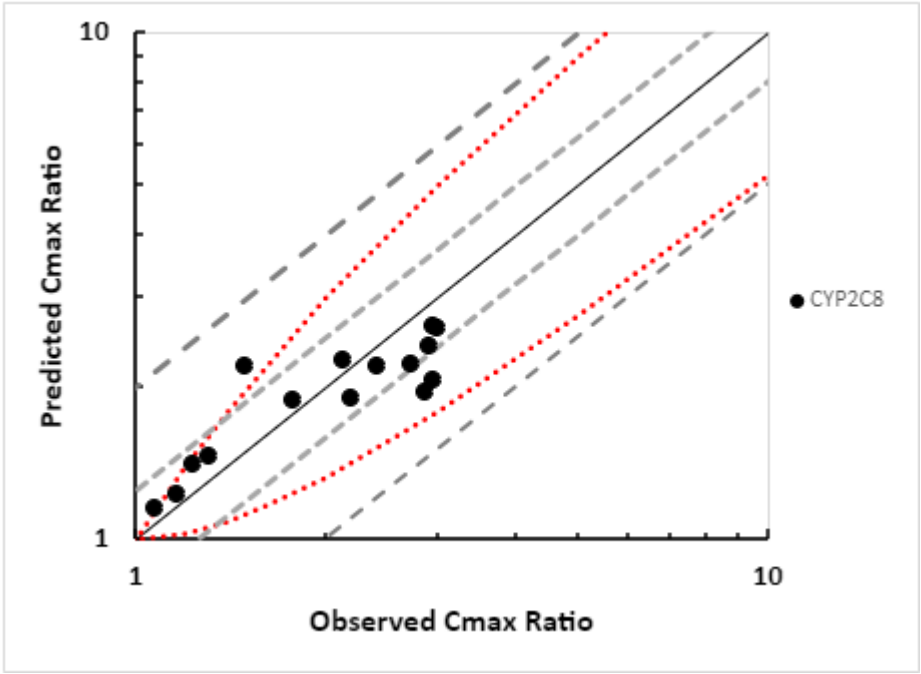
For CYP3A4/5 (n=114), the prediction accuracy was good with an AFE of 0.93 and 0.95 and an AAFE of 1.22 and 1.27 for C_{max} and AUC, respectively. The predictions were within 1.5-fold of observed C_{max} ratios for all except 9 of the interactions where 2 of these also fell outside 2-fold of the observed C_{max} ratio. The AUC ratio was predicted well with 81% of the predictions falling within 1.5-fold of the observed data, only 2 predictions were outside of 2-fold from the observed AUC ratio for simulations with quinidine and erythromycin, and simvastatin and erythromycin.

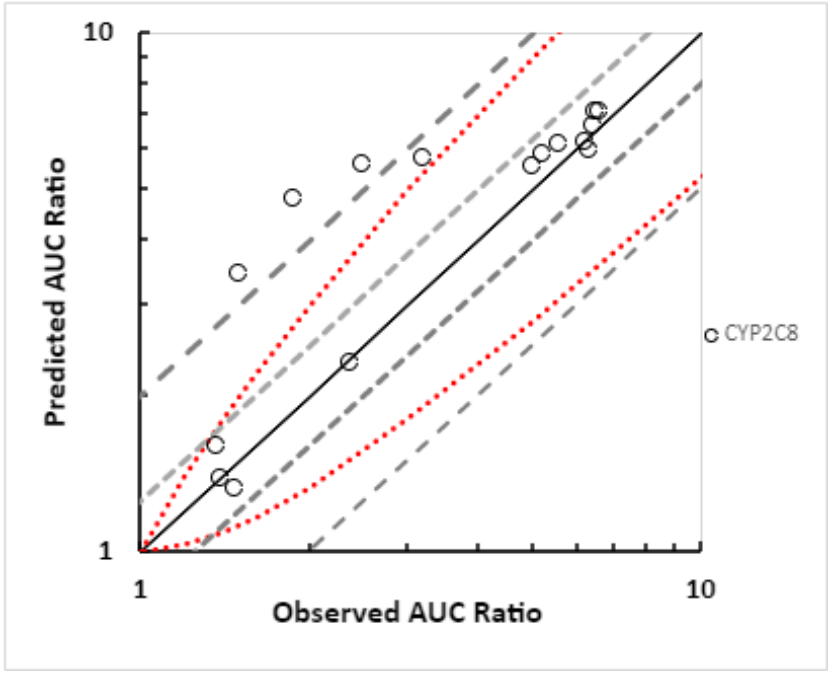




CYP1A2	V19R1	
	Cmax Ratio	**AUC Ratio**
AFE (bias)	0.91	1.03
AAFE (precision)	1.21	1.21
Number Studies	15	20
Number Studies	15	20

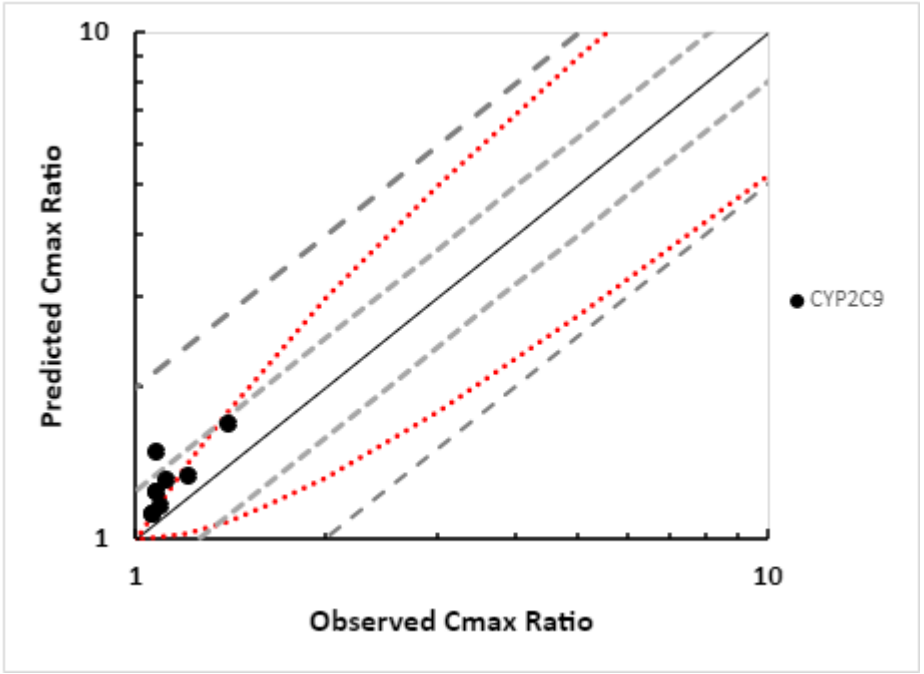
Figure 6. Predicted *versus* observed CYP1A2-mediated DDIs

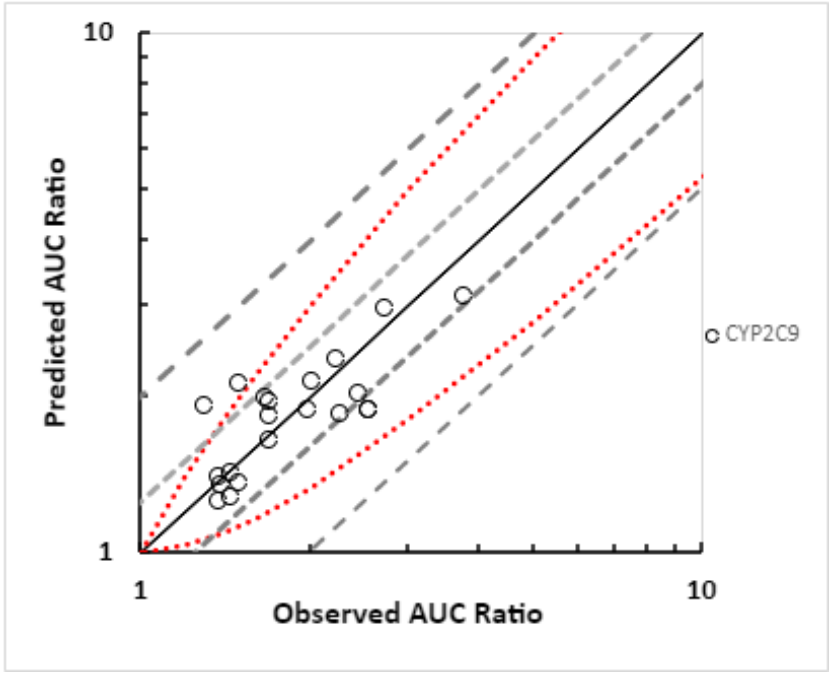




CYP2C8	V19R1	
	Cmax Ratio	**AUC Ratio**
AFE (bias)	1.08	0.81
AAFE (precision)	1.19	1.28
Number Studies	16	16
Number Studies	16	16

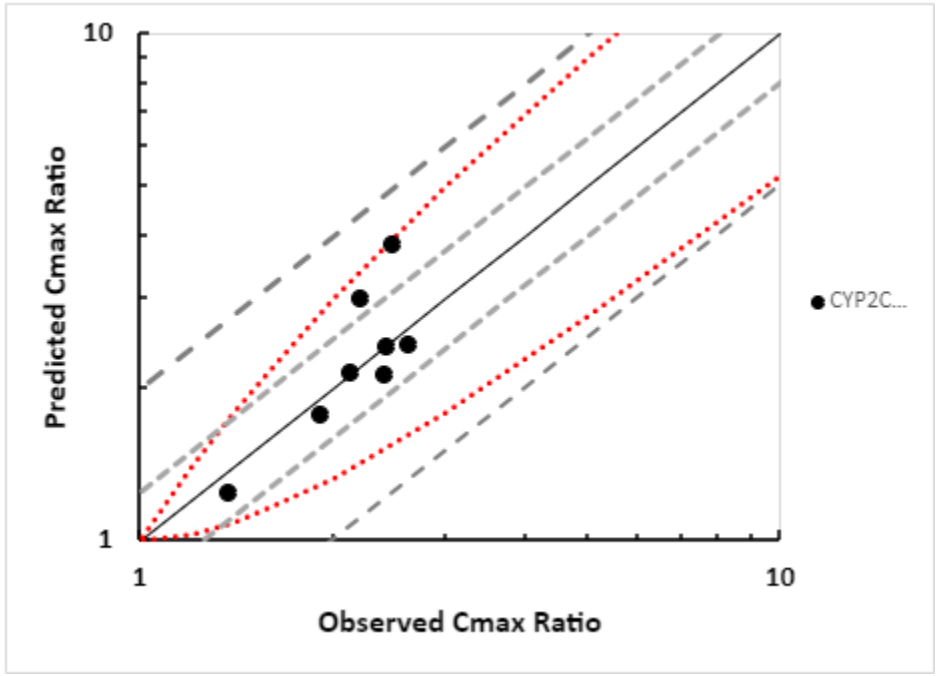
Figure 7. Predicted *versus* observed CYP2C8-mediated DDIs

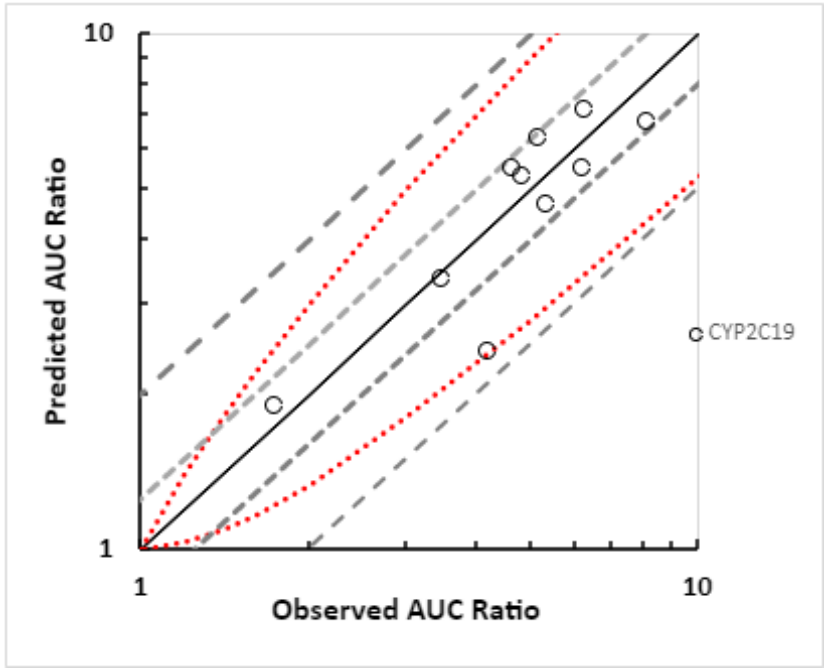




CYP2C9	V19R1	
	Cmax Ratio	**AUC Ratio**
AFE (bias)	0.89	1.03
AAFE (precision)	1.13	1.15
Number Studies	9	21
Number Studies	9	21

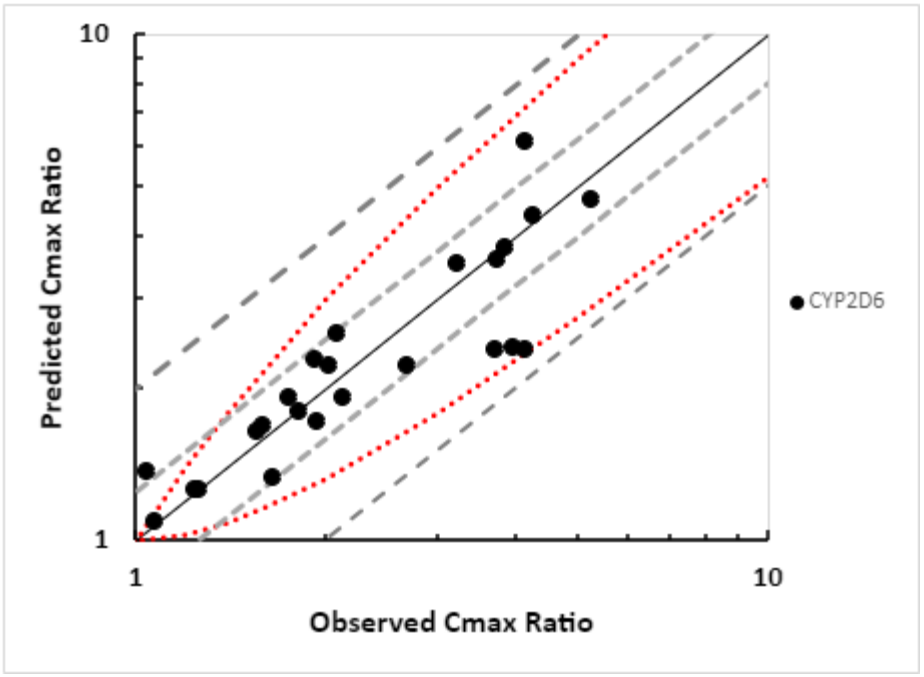
Figure 8. Predicted *versus* observed **CYP2C9-mediated** DDIs

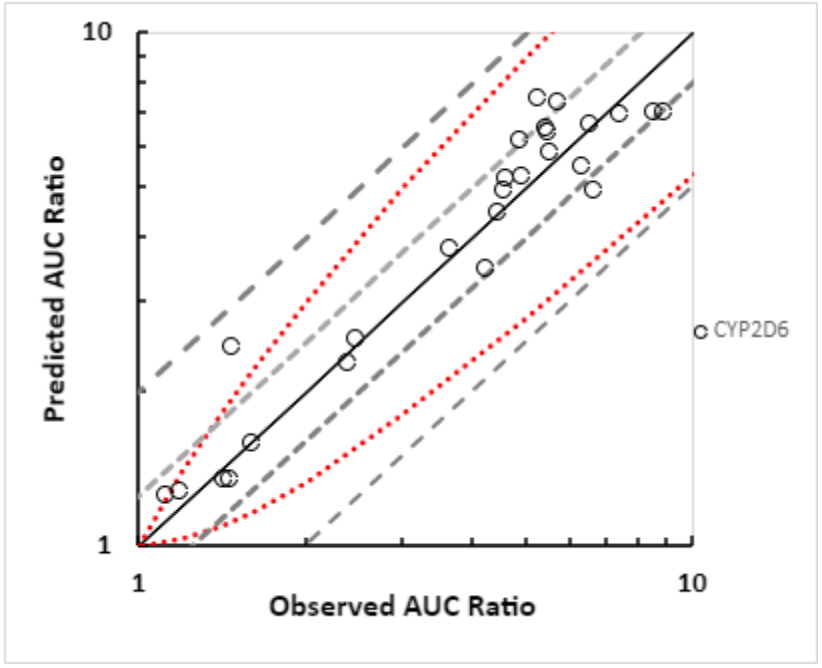




CYP2C19	V19R1	
	Cmax Ratio	**AUC Ratio**
AFE (bias)	0.97	1.05
AAFE (precision)	1.16	1.18
Number Studies	8	11
Number Studies	8	11

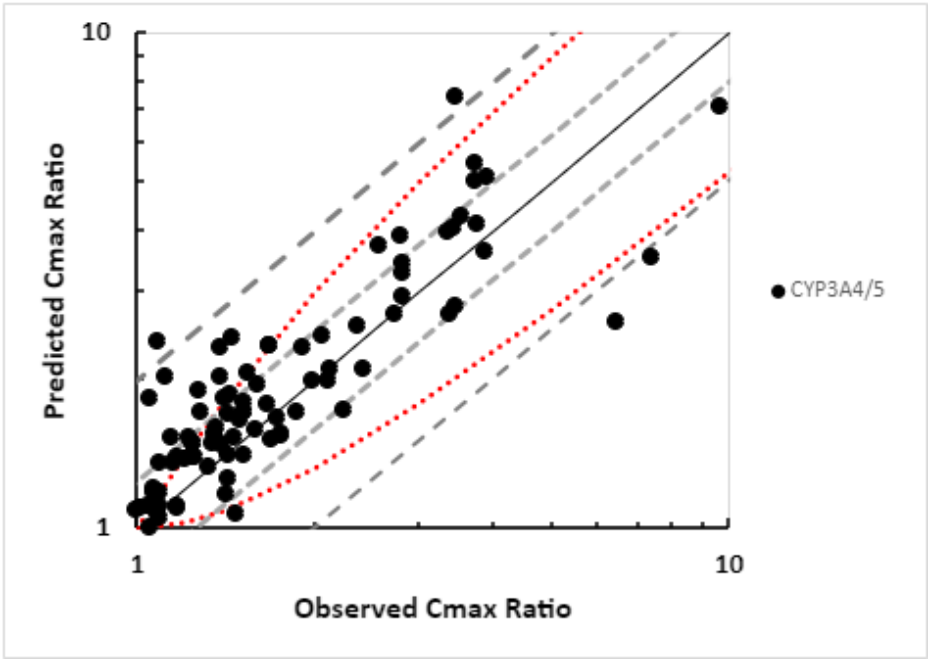
Figure 9. Predicted *versus* observed **CYP2C19-mediated** DDIs

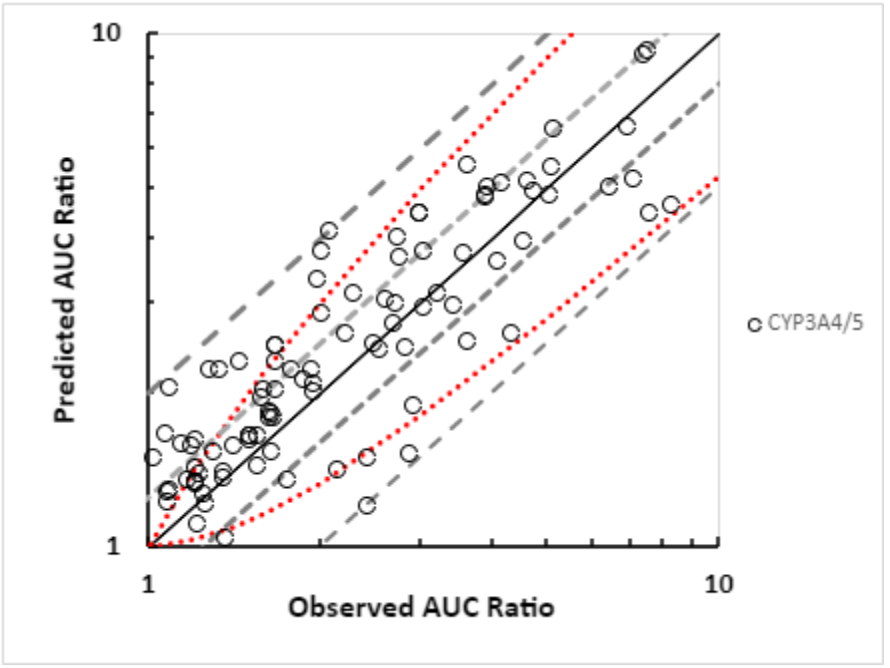




CYP2D6	V19R1 Built 96	
	Cmax Ratio	**AUC Ratio**
AFE (bias)	1.05	0.96
AAFE (precision)	1.17	1.04
Number Studies	25	28
Number Studies	25	28

Figure 10. Predicted *versus* observed **CYP2D6-mediated** DDIs





CYP3A4	V19R1	
	Cmax Ratio	**AUC Ratio**
AFE (bias)	0.93	0.95
AAFE (precision)	1.22	1.27
Number Studies	95	114
Number Studies	95	114

Figure 11. Predicted *versus* observed **CYP3A4-mediated** DDIs

6. Version comparisons

In this analysis, we identified a DDI matrix involving substrates and inhibitors of CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 which was then used for qualification of the Simcyp Simulator (V19R1). In total, 33 substrates and 24 inhibitors were identified for inclusion in the DDI qualification matrix. Compound file summaries have been prepared for each of these compounds in V19 R1 (Appendix 2).

In addition to providing details relating to input parameters and PK predictions, the compound file summaries also contain examples of DDI predictions. These summaries have been generated in later versions of the Simcyp Simulator, including V20 and V21.

If new data become available for compounds, the files within the Simcyp Simulator are updated especially if they improve the performance of the models. Thus, any differences in PK and DDI predictions for a compound may be a consequence of changes in compound file parameters or system parameter updates.

Thus, two sets of comparisons are typically performed. Compound files developed in a new version e.g. V20 files in the V20 simulator would be compared against V20 files in the V19 simulator – this comparison gives an indication of the impact of the changes in compound files. In addition, V20 files in the V20 simulator would be compared against V19 files in the V19 simulator. This comparison would reflect changes in system parameters as well as changes in compound files. The former has been provided for V19/V20 and the latter for V20/V21 (Appendix 6). The changes in compound files which are shown in Appendix 7 are negligible as can be seen by the graphs shown in Appendix 6.

7. Summary and Key Findings

For an investigational new drug (IND), the CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 inhibitors presented here can be used with confidence to assess the CYP-mediated drug interaction potential of novel drugs as victims. However, it is important to recognise, that during model development, for most of the substrates included in the DDI qualification matrix, a clinical DDI study was used to optimise their fmCYP values and was then verified using an independent clinical DDI study (if available). Thus, for drugs in development, even though initial simulations can be carried out to assess the DDI potential as victim drugs, it is likely that a clinical DDI study with a strong inhibitor (typically) or mass balance study is warranted to refine the relative contributions of clearance routes.[1] Thereafter, the qualification dataset described herein indicate that PBPK modelling can be used to support untested DDI scenarios involving moderate or weak inhibitors of the relevant CYP enzyme as has typically been the case.[11]

The results presented here indicate that the CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 substrates included in this analysis can be applied with confidence to assess the CYP-mediated drug interaction potential of novel drugs as perpetrators. Firstly, as performed here, it is essential to demonstrate that the PBPK model developed for the perpetrator is able to capture the observed plasma concentration-time profiles and PK parameters at clinically relevant doses.

Secondly, the *in vitro* determined inhibitory parameters of the drug may require some calibration or optimisation, prior to assessing the DDI potential of the compound, as described below. Thus, the qualification dataset described here, indicate that PBPK modelling can be used to support untested scenarios (co-medications and less sensitive substrates) for perpetrators of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 typically when a clinical study has been performed to assess the DDI potential of the drug using a sensitive substrate, thus allowing optimisation of the relevant *in vitro* inhibitory parameters if needed.

In addition to inactivation parameters for the inhibitors, estimates of enzyme turnover in the liver (k*deg*) are required for DDI predictions. *In vivo* enzyme levels are governed by the rates of *de novo* enzyme synthesis and degradation which differ for CYP enzymes and thus, result in different enzyme turnovers.[21]Thus, it is important to indicate which values were used for each enzyme; values were 0.0183 (CYP1A2), 0.0301 (CYP2C8), 0.0067 (CYP2C9), 0.0267 (CYP2C19), 0.0099 (CYP2D6) and 0.0193 h-*1* (CYP3A4).

Based on the predictive performance of the platform, the data presented here demonstrate that Simcyp Simulator (V19 R1) can be applied with reasonably accuracy to assess the CYP-mediated DDI potential of investigational new drugs (IND) as victim or perpetrators involving competitive inhibition or MBI.

8. Questions for EMA

Question 1: Does the Agency agree that the results presented here support our proposed COU statements for using the Simcyp Simulator V19 R1 to predict the DDI potential of drugs as victims or perpetrators of CYP-mediated interactions involving competitive inhibition or MBI for untested clinical DDI scenarios?

Certara UK Ltd Position: Certara UK Ltd believes that the results from our data analysis and that published previously[12], establish the high predictive accuracy of the Simcyp Simulator V19 R1 for clinical trial outcomes involving CYP-mediated inhibition. The platform can be used to optimise dose(s) and dosing schedules for the drug itself or drugs that are likely to be co-prescribed. In addition to the analysis presented here, the Simcyp Simulator has been applied to assess the DDI potential of drugs in development and the results have been used to inform clinical DDIs in the label.[1]

Question 2: What steps are needed for qualification of subsequent versions of the Simcyp Simulator?

Certara UK Ltd Position: A full analysis was conducted for the Simcyp Simulator V19 R1. Supporting documentation in the form of comparisons of outputs of PK parameters generated from compound files run in V19 *versus* v20 *versus* V21 are routinely generated. Furthermore, compound files summaries for each compound are generated in V19, V20 and V21. These could be used to support qualification of CYP-mediated inhibition in V20 and V21 in addition to examples that have been published using V20 and V21 of the platform.

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10.Appendix 1.

Scaling Methods and PBPK Models

10.1 Physiologically based pharmacokinetic models

A minimal physiologically based pharmacokinetic (PBPK) model, which considers both liver and intestinal metabolism (Figure A), is incorporated in the Simcyp Simulator. It includes a single adjusting compartment (SAC) that lumps all tissues excluding the intestine, liver and portal vein and can be used to represent those organs that make a significant contribution to the volume of distribution. The model can also be expanded to a full PBPK model by inclusion of additional tissues such as adipose, brain, bone, heart, lung, muscle and skin (Figure A2).

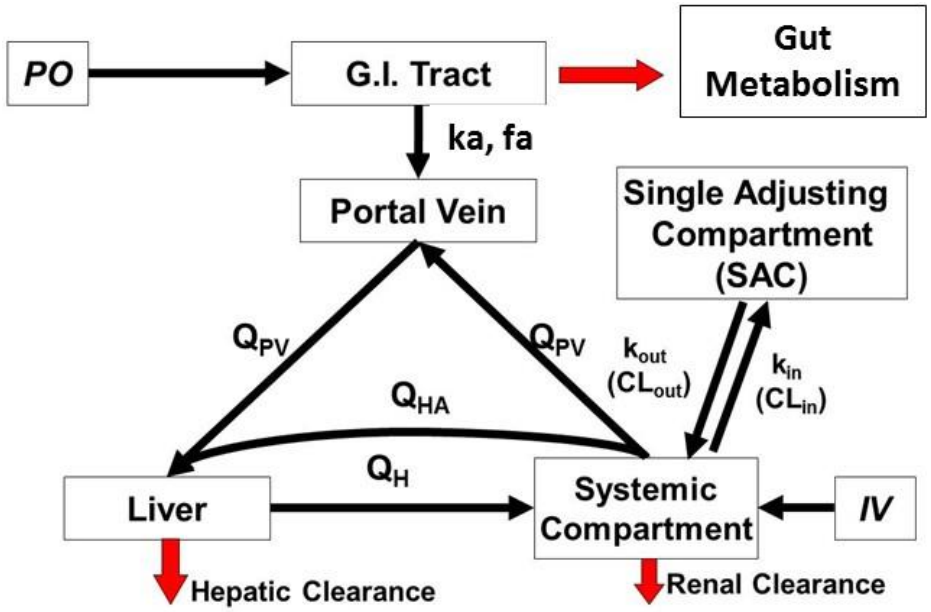

Figure A1. Minimal physiologically based pharmacokinetic model with single adjusting compartment. Q_H, Q_{PV}, and Q_{HA} are blood flows in the liver, portal vein, and hepatic artery, respectively; k_{in} and k_{out} are first order rate constants which act on the masses of drug within the systemic compartment and the SAC respectively; IV and PO are intravenous and oral dosing routes respectively; fa and ka are the fraction absorbed and the first order absorption rate constant, respectively.

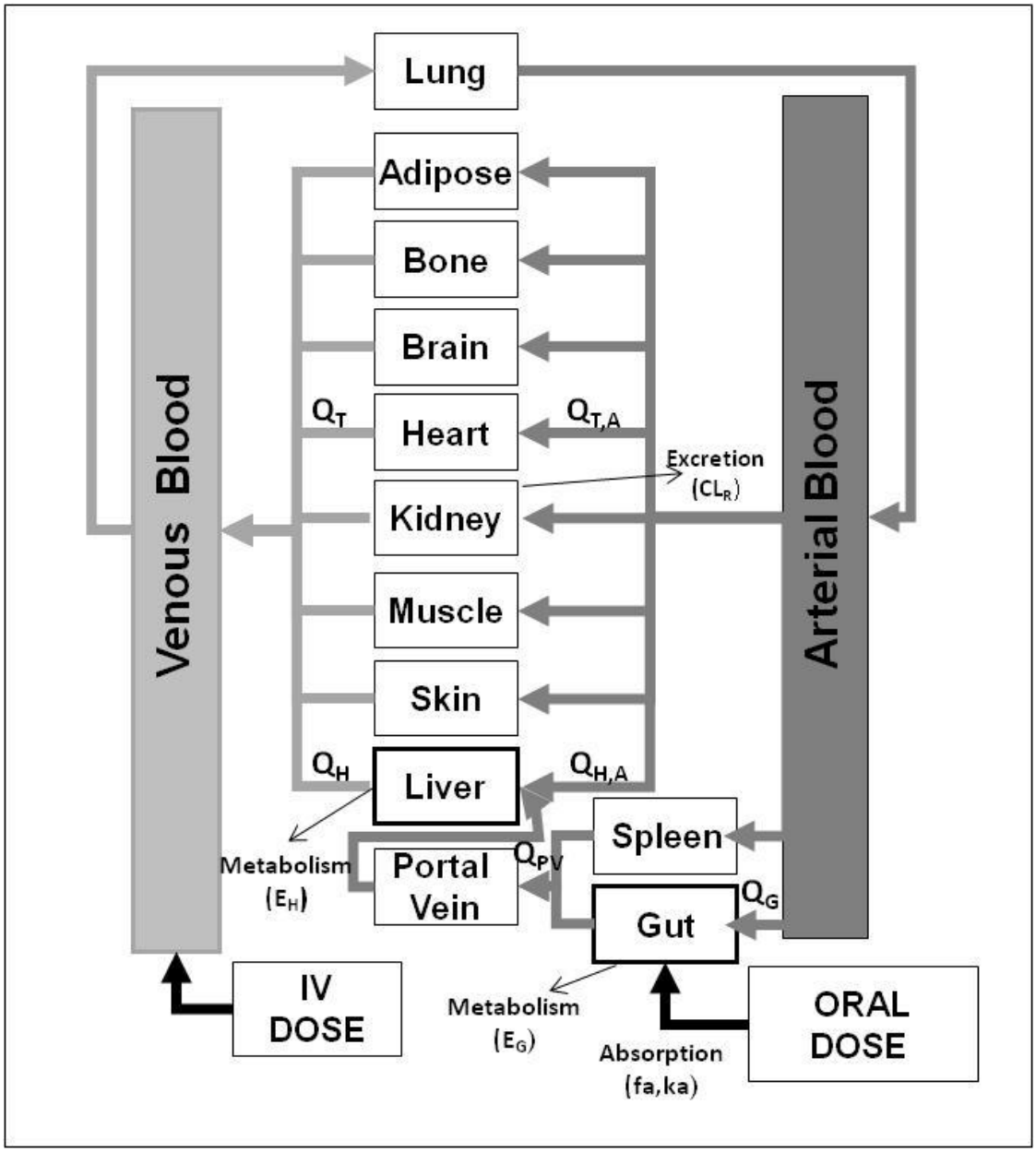

Figure A2. A physiologically based pharmacokinetic model. Q_H, $Q_{H,A}$, Q_{PV}, Q_G, $Q_{T,A}$ and Q_T are blood flows in the hepatic vein, hepatic artery, hepatic portal vein, gut and blood flows into and out of the other tissue (T) compartments, respectively; E_G and E_H are the fractions undergoing first pass metabolism in the gut and liver, respectively; CL_R is the renal clearance; fa and ka are the fraction absorbed and the first order absorption rate constant, respectively.

10.2 Prediction of V_{ss}

For the minimal model, an *in vivo* V_{ss} value (and associated variability) can be used as an input or this parameter can be predicted using Equation 1 from Sawada *et al*. (1984):

$$V_{ss} = (\sum V_t \times P_{t:p}) + (V_e \times E:P) + V_p \quad \text{(Equation 1)}$$

Where V is the fractional body volume (L/kg) of a tissue (t), erythrocyte (e), and plasma (p), E:P is the erythrocyte:plasma ratio and $P_{t:p}$ is the partition coefficient for non-adipose and adipose components. Three methods are available for prediction of $P_{t:p}$, the first reported by Poulin and Theil (2002) and modified by Berezhkovskiy (2004) and the second by Rodgers and Rowland (2006). The third method extends the Rodgers and Rowland method to account for the impact of membrane potential on the permeation of ionised drugs using the Fick-Nernst-Planck equation (Gaohua *et al.*, 2016).

10.3 Absorption Models

Several absorption models are available within the Simcyp Simulator including a first-order absorption model and the advanced dissolution absorption metabolism (ADAM) model (Jamei *et al.,* 2009).

10.4 Prediction of first order absorption (fa) and associated rate constant (ka)

For the fraction absorbed (fa) and first order absorption rate constant (ka), *in vivo* values and associated variability can be used as inputs. Alternatively, Equation 2 and Equation 3 can be used to predict fa and ka from an estimate of *in vivo* permeability, $P_{eff,man}$, (Yu *et al*., 1998). Several methods can be used within the Simcyp Simulator to predict $P_{eff,man}$ for a given drug. These are based on apparent permeability data obtained with cell lines (Caco-2, MDCK, LLC-PK1) (Sun *et al.,* 2002, Tchaparian *et al*., 2008), the PAMPA system or from QSAR based on physicochemical properties (PSA and HBD, Winiwarter *et al.,* 1998).

$$ka = \frac{2 \times P_{eff,man}}{R} \quad \text{(Equation 2)}$$

$$fa = 1 - (1 + 0.54\ P_{eff,man})^{-7} \quad \text{(Equation 3)}$$

10.5 Prediction of Clearance

Clearance (CL) can be predicted from either human liver microsome (HLM) data or from human hepatocyte (HHep) data using Equation 4 and Equation 5.

$$CLu_{\text{int}H-pe} = \frac{CL_{\text{int}-pe}}{fu_{mic-pe}} \times Uptake \times MPPGL \times LiverWt \times 60 \times 10^{-6} \quad \text{(Equation 4)}$$

$$CLu_{\text{int}H-pe} = \frac{CL_{\text{int}-pe}}{fu_{inc-pe}} \times Uptake \times HPGL \times LiverWt \times 60 \times 10^{-6} \quad \text{(Equation 5)}$$

Where $CL_{intH\text{-}pe}$ is the CL in HLM by pathway 'p' by enzyme 'e' per mg microsomal protein, or CL in HHep by pathway 'p' by enzyme 'e' per million cells, MPPGL is the amount (mg) of microsomal protein per gram of liver, HPGL is the total number (in million) of hepatocytes per gram of liver, fu_{mic} is the free fraction of drug in the microsomal incubation, fu_{inc} is the free fraction of drug in the hepatocyte incubation, 'Uptake' is a factor that accounts for any active hepatic uptake (default value = 1) and 'LiverWt' is the liver weight of an individual, '60 x 10^{-6}' is a unit conversion factor.

Hence, total unbound intrinsic hepatic clearance ($CLu_{int,H\text{-}pe}$) is given by the sum of all intrinsic clearances by all enzymes and pathways (Equation 6).

$$CLu_{\text{int},H} = \sum_{p=1}^{n}\sum_{e=1}^{m} CLu_{\text{int},H-pe} \quad \text{(Equation 6)}$$

Where n is the number of pathways and m is the number of enzymes involved in the metabolism of the substrate. This intrinsic clearance value is applied in association with a prediction of drug distribution and through a number of differential equations (PBPK model) to generate a plasma drug concentration-time profile.

10.6 Prediction of First Pass Metabolism in the Gut (F_G)

To estimate intestinal availability (F_G), a model of 'first pass' metabolism, similar to the 'well-stirred liver', (Rostami-Hodjegan and Tucker, 2004) is used for substrates metabolised primarily by CYP3A but also by CYP2D6, CYP2C9 and CYP2C19 (Equation 7). In contrast to the 'well-stirred' liver model, the flow term (Q_{gut}) represents a nominal blood flow and is a hybrid parameter reflecting drug absorption rate from the gut lumen, removal of drug from the enterocyte by the enterocytic blood supply and the volume of enterocytes. The free fraction of drug within the enterocyte is represented by the fu_{gut} term.

$$F_G = \frac{Q_{gut}}{Q_{gut} + fu_{gut} \times CL_{uG,int}} \quad \text{(Equation 7)}$$

The Q_{gut} term can be expanded in terms of its fundamental parameters:

$$Q_{gut} = \frac{Q_{villi} \text{ x } CL_{perm}}{Q_{villi} + CL_{perm}} \quad \text{(Equation 8)}$$

Where Q_{villi} is the villous blood flow (6% of the cardiac output in the Simulator) and CL_{perm} is a clearance term defining the permeability through the enterocyte.

$$CL_{perm} = P_{eff,man} \text{ x } A \quad \text{(Equation 9)}$$

CL_{perm} is the product of the value for effective intestinal permeability in man ($P_{eff,man}$) and A is the net cylindrical surface area of the small intestine (Yang *et al*., 2007).

In the absence of any information on active drug uptake into the enterocyte, fu_{gut} is set at a default value of 1 (which assumes that there is insufficient time for plasma protein binding equilibrium or erythrocyte uptake before the drug is removed from the basolateral side of the enterocyte). However, it may also be set at fu_p which assumes that there is sufficient time for plasma protein binding equilibrium. Assuming that a proportional relationship exists between Q_{gut} and permeability (P_{app}) data obtained using Caco-2 cells, a Q_{gut} value can be estimated (Yang *et al.,* 2007). For calculation of gut intrinsic clearance ($CLu_{G,int}$), the CYP3A-mediated hepatic CLu_{int} is divided by the abundance of CYP3A in liver (137 pmol P450/mg protein) to obtain the CLu_{int} in terms of µl/min per pmol P450. Using a mean abundance of 70000 pmol CYP3A/total gut this value is scaled to a whole gut CLu_{int} value (Yang *et al*., 2004). The assumption that the intrinsic clearance per pmol CYP is the same in both gut and liver is supported by observations on a number of drugs, such that hepatic rather than intestinal microsomal data can be used (Yang *et al*., 2004).

10.7 Prediction of F_H and F

The 'well-stirred' model of hepatic clearance was used to estimate the fraction avoiding first-pass metabolism in the liver (F_H).

$$F_H = \frac{Q_H}{Q_H + fu_B \times CLu_{H.\text{int}}} \quad \text{(Equation 10)}$$

where Q_H (hepatic blood flow), fu_B (the fraction of drug unbound in blood) and $CLu_{H,int}$ (intrinsic metabolic clearance) are the primary determinants of net hepatic clearance (CL_H). Thus, following oral administration, bioavailability F can be estimated using Equation 11:

$$F = fa.F_G.F_H \quad \text{(Equation 11)}$$

10.8 Enzyme Dynamics and Inhibition

Changes in metabolic clearance due to reversible inhibition of enzyme activity, or changes in enzyme levels due to mechanism-based inactivation and/or induction can be handled using mechanistic dynamic models within the Simcyp Simulator. The underlying assumptions and operating differential equations have been described in detail elsewhere (Rowland Yeo *et al*., 2010; Rowland Yeo *et al*., 2011). Unbound concentrations of inhibitor in the liver and portal vein are used as the driving force for inhibition of metabolism in the liver and gut, respectively. Values of the intrinsic turnover of hepatic and gut CYP3A4 (k_{deg}) used in the simulations involving induction of CYP3A4 by rifampicin were 0.019 h^{-1} and 0.03 h^{-1}, respectively (Rowland Yeo *et al.,* 2011; Yang *et al*., 2008).

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11.Appendix 2.

Compound File Summaries

In total, 33 substrates and 24 inhibitors were identified for inclusion in the DDI matrix for qualification of CYP-mediated inhibition using the Simcyp Simulator (V19R1). Compound file summaries for each substrate and inhibitor relevant to V19 R1 can be found within the corresponding document cited below. The input parameters for each compound, predicted PK

parameters and verification of DDI as substrates and inhibitors are indicated within each compound file summary, all of which are saved in the accompanying documents shown below.

Inhibitor Summaries

Substrate Summaries

12.Appendix 3.

Inhibitor Characteristics

Table A1. Inhibitor information from Simcyp Simulator compound files (V19R1) showing classification, interaction parameters and driving mechanism of the interactions.

Inhibitor		FDA Classification	$K_{i,u}$ (µM)	K_{app} (µM)	K_{inact} (1/h)	Driving Mechanism	In Vitro/ Optimised	Ref
Ciprofloxacin	CYP1A2	Strong	1.84*	-	-	Competitive	Optimised	(1)
Fluvoxamine	CYP1A2	**Strong**	0.002*	-	-	Competitive	Optimised	**
Gemfibrozil	CYP2C8	**Strong**	24.1	-	-	MBI	In Vitro	(2-4)
Gemfibrozil 1-O-β Glucuronide	CYP2C8	-	4.88	27.1*	6.5*	-	-	(2-6)
Trimethoprim	CYP2C8	Weak	8.47	-	-	Competitive	In Vitro	(4)
Amiodarone	CYP2C9	Moderate	0.425	0.028	0.6	MBI	In Vitro	(7, 8)
Mono-desethyl Amiodarone	CYP2C9	-	0.120	-	-	-	-	(7, 8)
Fluconazole	CYP2C9	**Moderate**	20.4	-	-	Competitive	In Vitro	(9)
Fluvoxamine	CYP2C9	Weak	0.126	-	-	Competitive	Optimised	**
Sulphaphenazole	CYP2C9	-	1.5*	-	-	Competitive	Optimised	(10)
Fluvoxamine	CYP2C19	**Strong**	0.006*	-	-	Competitive	Optimised	**
Fluoxetine	CYP2C19	Strong	9.39	2.69	2.16	MBI	In Vitro	(11)
Nor-Fluoxetine	CYP2C19	-	2.99	6*	3.27	MBI	Optimised	(11-13)
Ticlopidine	CYP2C19	Strong	-	0.432	4.43	MBI	In Vitro	(14)
Bupropion	CYP2D6	-	0.084*	-	-	Competitive	Optimised	(15)
OH-Bupropion	CYP2D6		0.053*	-	-	Competitive	Optimised	(15)
Cinacalcet	CYP2D6	Moderate	0.0006	-	-	Competitive	In Vitro	#
Fluoxetine	CYP2D6	**Strong**	0.012	-	-	Competitive	In Vitro	(16)
Fluvoxamine	CYP2D6	Weak	0.189*	-	-	Competitive	Optimised	**
Paroxetine	CYP2D6	**Strong**	0.46	0.137	10.2	MBI	In Vitro	(8, 17-24)
Quinidine	CYP2D6	Strong	0.0119	-	-	Competitive	In Vitro	(25)
Ritonavir	CYP2D6	Weak	0.04*	-	-	Competitive	Optimised	(26)
Amiodarone	CYP3A4	-	4.41	0.052	0.8	MBI	In Vitro	(7, 8)
Mono-desethyl Amiodarone	CYP3A4	-	0.482	-	-	-	-	(7, 8)
Aprepitant	CYP3A4	Moderate	1##	2.66##	6##	MBI	In Vitro	(27)
Atazanavir	CYP3A4/5	-	2.35	0.84	3	MBI	In Vitro	(28)
Cimetidine	CYP3A4	Weak	25*	-	-	Competitive	Optimised	(29)
Clarithromycin	CYP3A4	**Strong**	8.7	12	2.13	MBI	In Vitro	(30, 31)
Cyclosporine	CYP3A4	Moderate	0.89	-	-	Competitive	In Vitro	(32)
Diltiazem	CYP3A4/5	Moderate	36.1	4.75	0.70	MBI	In Vitro	(31, 33)
Desmethyl-Diltiazem	CYP3A4/5	-	2.43	1.74	1.09	-	-	(31, 33)
Erythromycin	CYP3A4	**Moderate**	29.8	17.64	2.25*	MBI	Optimised	(34)
Fluconazole	CYP3A4	**Moderate**	10.7	-	-	Competitive	In Vitro	(35)
Fluconazole	CYP3A5	**Moderate**	84.6	-	-	Competitive	In Vitro	(35)
Fluoxetine	CYP3A4	-	3.64	16	0.66	MBI	In Vitro	(11)
Fluvoxamine	CYP3A4	Moderate	0.789*	-	-	Competitive	Optimised	**
Fluvoxamine	CYP3A5	Moderate	5.82*	-	-	Competitive	Optimised	**
Itraconazole	CYP3A4	**Strong**	0.0023	-	-	Competitive	In Vitro	(36)
Ketoconazole	CYP3A4	Strong	0.0146	-	-	Competitive	In Vitro	(35)

Ketoconazole	CYP3A5	Strong	0.105	-	-	Competitive	In Vitro	(35)
Quinidine	CYP3A4	-	5.1	-	-	Competitive	In Vitro	(37)
Ritonavir	CYP3A4/5	Strong	0.0019	0.18	19.8	MBI	In Vitro	(38)
Verapamil	CYP3A4	**Moderate**	-	2.21	2	MBI	In Vitro	(31)
Verapamil	CYP3A5	**Moderate**	-	3.99	1.84	MBI	In Vitro	(39-41)
Norverapamil	CYP3A4	**Moderate**	-	10.3	18	MBI	In Vitro	(16)
Norverapamil	CYP3A5	**Moderate**	-	4.53	4.2	MBI	In Vitro	(16)

* Optimised value, # Measured Value, ##fu,mic was recalculated in the Simcyp Simulator

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13.Appendix 4.

Study Design and Results of DDI Simulations

Table A2. Study design, observed and predicted AUC and C_{max} ratios using Simcyp Simulator V19R1To

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
1	(1)	CYP3A4/5	Alfentanil 15 µg/kg single iv (3 hr after fluconazole)	Fluconazole, 100 mg (single oral)	-	1.2	-	1.27	**-**	**1.06**
2	(1)	CYP3A4/5	Alfentanil 40 µg/kg single oral (3 hr after fluconazole)	Fluconazole, 100 mg (single oral)	1.16	2	1.42	1.68	**1.22**	**0.84**
3	(1)	CYP3A4/5	Alfentanil 15 µg/kg single iv (3 hr after fluconazole)	Fluconazole, 200 mg (single oral)	-	1.6	-	1.52	**-**	**0.95**
4	(1)	CYP3A4/5	Alfentanil 40 µg/kg single oral (3 hr after fluconazole)	Fluconazole, 200 mg (single oral)	1.53	3.1	1.76	2.37	**1.15**	**0.74**
5	(1)	CYP3A4/5	Alfentanil 15 µg/kg single iv (3 hr after fluconazole)	Fluconazole, 400 mg (single oral)	-	2.2	-	1.95	**-**	**0.89**
6	(1)	CYP3A4/5	Alfentanil 40 µg/kg single oral (3 hr after fluconazole)	Fluconazole, 400 mg (single oral)	1.72	5.5	2.25	3.66	**1.31**	**0.67**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
7	(2)	CYP3A4/5	unlabelled d0-Alfentanil 0.5 mg iv on day 4 (assuming at 7:00 AM)	Ketoconazole, 400 mg (oral) for 3 days at bedtime (3 doses, assuming at 11:30 PM)	-	4.8	-	3.93	**-**	**0.82**
8	(2)	CYP3A4/5	deuterium-labelled d3-Alfentanil 1 mg oral on day 4 (assuming at 10:00 AM)	Ketoconazole, 400 mg (oral) for 3 days at bedtime (3 doses, assuming at 11:30 PM)	2.8	9.2	3.47	7.58	**1.24**	**0.82**
9	(2)	CYP3A4/5	unlabelled d0-Alfentanil 0.5 mg iv on day 5 (assuming at 7:00 AM)	Ketoconazole, 400 mg (oral) for 4 days at bedtime (4 doses, assuming at 11:30 PM)	-	5.0	-	3.95	**-**	**0.79**
10	(2)	CYP3A4/5	deuterium-labelled d3-Alfentanil 1 mg oral on day 5 (assuming at 7:00 AM)	Ketoconazole, 400 mg (oral) for 4 days at bedtime (4 doses, assuming at 11:30 PM)	5.07	12.0	3.93	10.14	**0.78**	**0.85**
11	(3)	CYP3A4/5	Alprazolam, 1 mg SD (day 3), (1 h after 5th Ketoconazole dose)	Ketoconazole, 200 mg BID for 4 days (8 doses)	1.1	3.98	1.1	2.75	**1.0**	**0.69**
12	(4)	CYP3A4/5	Alprazolam, 0.5 mg SD (day 4)	Ketoconazole, 200 mg BID for 6 days (12 doses)	1.18	2.91	1.09	3.07	**0.92**	**1.05**
13	(4)	CYP3A4/5	Alprazolam, 0.5 mg SD (day 4)	Ketoconazole, 200 mg QD for 6 days (6 doses)	1.18	2.7	1.1	2.71	**0.93**	**1.00**
14	(5)	CYP3A4/5	Alprazolam, 0.8 mg SD (day 8)	Erythromycin, 400 mg TID for 10 days (30 doses)	1.18	2.47	1.07	2.49	**0.91**	**1.01**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
15	(6)	CYP3A4/5	Alprazolam, 1 mg SD (day 2) RTV summary (At 8.30am)	Ritonavir, 200 mg 4 doses over 3 days at 4pm d1, 7.30am and 4.30pm D2, 9am D3	1.04	2.48	1.1	3.64	**1.06**	**1.47**
16	(7)	CYP3A4/5	Alprazolam, 1 mg SD on day 22	Fluoxetine, 20 mg QD for 24 days	1.09	1.32	1.02	1.22	**0.94**	**0.92**
17	(8)	CYP3A4/5	Alprazolam, 0.5 mg TID for 7 days and morning dose on day 8	Cimetidine, 200 mg TID with 400mg at night for 9 days	1.82	1.64	1.06	1.08	**0.58**	**0.66**
18	(9)	CYP3A4/5	Aprepitant, 125 mg SD day 5	Ketoconazole, 400 mg QD for 10 days	1.52	4.78	1.47	3.93	**0.97**	**0.82**
19	(10)	CYP3A4/5	Atazanavir, 400 mg QD for 13 days	Ketoconazole, 200 mg QD days 7 – 13	0.98	1.1	1.19	1.23	**1.21**	**1.12**
20	(11)	CYP3A4/5	Atazanavir, 400 mg QD for 10 days	Clarithromycin, 500mg BID days 7 – 10	1.06	1.28	1.09	1.1	**1.02**	**0.86**
21	(11)	CYP3A4/5	Clarithromycin, 500 mg BID days 7 – 10	Atazanavir, 400 mg QD for 10 days	1.5	1.94	1.37	1.59	**0.91**	**0.82**
22	(12)	CYP3A4/5	Clarithromycin, 500 mg BID for 4 days (8 doses)	Ritonavir, 200 mg TID for 4 days (12 doses)	1.54	1.86	1.76	2.95	**1.1**	**1.52**
23	(13)	CYP3A4/5	Dexamethasone, 4.5 mg Day 4 at 9am	Itraconazole, Capsule 200 mg QD at 7.30 am on day 1-3 and 8am on day 4	1.58	3.69	1.59	3.59	**1.01**	**0.97**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
24	(14)	CYP3A4/5	Dexamethasone, 20 mg QD Day 1, 8 mg Day 2-5	Aprepitant, 125 mg QD day 1 (30 min before Dex), 80 mg QD day 2-5	1.52	2.2	1.15	1.34	**0.76**	**0.61**
25	(15)	CYP3A4/5	Dexamethasone, 20 mg QD Day 1, 8 mg Day 2-5	Aprepitant, 375 mg Day 1, 250 mg QD Day 2-5	1.82	4.1	1.41	2.1	**0.77**	**0.51**
26	(15)	CYP3A4/5	Dexamethasone, 12 mg QD Day 1, 4 mg Day 2-5	Aprepitant, 125 mg QD day 1, 80 mg QD Day 2-5	0.79	1.03	1.17	1.38	**1.48**	**1.34**
27	(15)	CYP3A4/5	Dexamethasone, 20 mg QD Day 1, 8 mg Day 2-5	Aprepitant, 40 mg QD Day 1, 25 mg QD Day 2-5	1.1	1.21	1.05	1.09	**0.95**	**0.90**
28	(16)	CYP3A4/5	Ibrutinib, 120 mg on Day 4 at 10 am	Ketoconazole, 400 mg QD Days 1-6 at 9 am	28.6	26.2	21.1	29.8	**0.74**	**1.14**
29	(17)	CYP3A4/5	Ibrutinib, 140 mg on Day 3 at 9 am (low fat fed)	Itraconazole, 200 mg BID Day 1 (8 am and 8 pm) and QD Days 2-3 (8 am)	8.8	10.2	10.2	14.1	**1.16**	**1.38**
30	(18)	CYP3A4/5	Midazolam, 7.5 mg SD (1 h after Fluconazole)	Fluconazole, 400 mg SD	2.3	3.73	1.91	3.05	**0.83**	**0.82**
31	(19)	CYP3A4/5	Midazolam, 7.5 mg SD (day 4)	Itraconazole, 200 mg QD for 4 days (8 doses)	3.41	10.77	2.82	9.97	**0.83**	**0.93**
32	(20)	CYP3A4/5	Midazolam, 15 mg SD (day 5)	Clarithromycin, 250 mg BID for 5 days (10 doses)	2.44	3.57	2.07	4.13	**0.85**	**1.16**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
33	[21]	CYP3A4/5	Midazolam, 15 mg SD (day 2), (1 h after 4th Diltiazem dose)	Diltiazem, 60 mg TID for 2 days (5 doses)	2.05	3.75	1.55	2.03	**0.76**	**0.54**
34	[21]	CYP3A4/5	Midazolam, 15 mg SD (day 2), (1 h after 4th Verapamil dose)	Verapamil, 80 mg TID for 2 days (5 doses)	1.97	2.92	2.12	3.46	**1.07**	**1.19**
35	[22]	CYP3A4/5	Midazolam, 6 mg SD (12 h after 1st Ketoconazole dose)	Ketoconazole, 200 mg BID for 2 days (3 doses)	4.24	16.0	3.56	12.56	**0.84**	**0.79**
36	[22]	CYP3A4/5	Midazolam, 2 mg IV SD (12 h after 1st Ketoconazole dose)	Ketoconazole, 200 mg BID for 2 days (3 doses)	-	5.1	-	4.67	**-**	**0.92**
37	[19]	CYP3A4/5	Midazolam, 7.5 mg SD (day 4)	Ketoconazole, 400 mg QD for 4 days (4 doses)	4.09	15.9	3.78	12.5	**0.92**	**0.79**
38	[23]	CYP3A4/5	Midazolam, 2 mg SD (day 5)	Ketoconazole, 400 mg QD for 5 days (5 doses)	5.42	13.96	3.76	12.12	**0.69**	**0.87**
39	[24]	CYP3A4/5	Midazolam, 2 mg SD oral coadministered with Aprepitant	Aprepitant, 250 mg SD	1.06	1.63	1.48	1.55	**1.40**	**0.96**
40	[24]	CYP3A4/5	Midazolam, 2 mg SD oral Aprepitant Day 8	Aprepitant, 250 mg SD Day 1	0.8	0.69	1.15	1.21	**1.44**	**1.75**
41	[25]	CYP3A4/5	Midazolam, 2 mg SD day 1 (1hr after Aprepitant)	Aprepitant, 125 mg day 1, 80 mg QD days 2-5	1.46	2.27	1.39	1.45	**0.96**	**0.64**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
42	[25]	CYP3A4/5	Midazolam, 2 mg SD day 1 (1hr after Aprepitant) Day 5	Aprepitant, 125 mg day 1, 80 mg QD days 2-5	1.94	3.3	1.61	1.99	**0.83**	**0.60**
43	[26]	CYP3A4/5	Midazolam, Midazolam 1.96 mg iv SD, 1hr after Aprepitant	Aprepitant, 125 mg SD	-	1.47	-	1.03	**-**	**0.7**
44	[27]	CYP3A4/5	Midazolam, Midazolam 2 mg iv SD day 4	Aprepitant, 125 mg day 1, 80 mg QD days 2-3	0.8	1.25	1.01	1.26	**1.26**	**0.99**
45	[27]	CYP3A4/5	Midazolam, Midazolam 2 mg iv SD day 8	Aprepitant, 125 mg day 1, 80 mg QD days 2-3	1.08	0.81	1.00	1.09	**0.93**	**1.35**
46	[28]	CYP3A4/5	Midazolam, 15 mg SD (Day 2) (30min after cimetidine)	Cimetidine, 400 mg BID (3 doses)	-	1.35	-	1.37	**-**	**1.01**
47	[29]	CYP3A4/5	Midazolam, 15 mg SD (2hrs after cimetidine)	Cimetidine, 400 mg SD	1.37	1.37	1.21	1.24	**0.88**	**0.91**
48	[30]	CYP3A4/5	Midazolam, 15 mg SD (Day 2) (2.5hr after cimetidine)	Cimetidine, 200 mg TID with 400 mg at night on day 1. 200 mg on day 2	2.38	2.02	1.09	1.1	**0.46**	**0.54**
49	[31]	CYP3A4/5	Midazolam, 15 mg on day 6	Erythromycin, 500 mg TID 7 days	2.7	4.42	2.75	7.59	**1.02**	**2.72**
50	[32]	CYP3A4/5	Midazolam, 10 mg SD on day 12 (1h after fluvoxamine)	Fluvoxamine, 50 mg BID days 1-6, 100 mg (73.3 mg free base) BID days 7-12	1.38	1.39	1.25	1.37	**0.91**	**0.99**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
51	[33]	CYP3A4/5	Midazolam, 7.5 mg SD day 4	Itraconazole, 100 mg QD for 4 days	2.56	5.47	2.38	4.99	**0.93**	**0.91**
52	[34]	CYP3A4/5	Midazolam, 7.5 mg SD day 4	Itraconazole, 200 mg QD for 4 days	2.91	5.16	2.82	7.15	**0.97**	**1.39**
53	[23]	CYP3A4/5	Midazolam, 2 mg SD	Ketoconazole, 400 mg SD	5.0	10.3	3.74	11.9	**0.75**	**1.16**
54	[35]	CYP3A4/5	Midazolam, 2 mg SD	Ketoconazole, 200 mg SD 2 hrs before MDZ	2.7	5.0	3.4	6.5	**1.26**	**1.30**
55	[36]	CYP3A4/5	Midazolam, 75 ug SD Day 3	Ketoconazole, 200 mg BID 2 days	3.7	6.5	2.6	5.2	**0.70**	**0.80**
56	[37]	CYP3A4/5	Midazolam, 3 mg day 4	Ritonavir, 30 mg for 5 days	-	3.89	-	4.59	**-**	**1.18**
57	[37]	CYP3A4/5	Midazolam, 3 mg day 4	Ritonavir, 100 mg for 5 days	-	6.51	-	6.98	**-**	**1.07**
58	[37]	CYP3A4/5	Midazolam, 3 mg day 4	Ritonavir, 300 mg for 5 days	-	9.01	-	7.45	**-**	**0.83**
59	[38]	CYP3A4/5	Midazolam, 1 mg IV Dose	Ritonavir, 200 mg for 11 days	-	4.9	-	4.7	**-**	**0.98**
60	[39]	CYP3A4/5	Midazolam, 3 mg SD on Day 2 (8 am)	Ritonavir, 100 mg at 6 pm day 1 and 7.30 am and 6 pm Day 2 (2 doses)	3.96	26.41	3.36	17.29	**0.85**	**0.65**
61	[40]	CYP3A4/5	Midazolam, 0.1 mg SD	Ritonavir, 100 mg BID	3.26	14.7	2.83	11.57	**0.87**	**0.79**
62	[41]	CYP3A4/5	Midazolam, 5 mg SD	Ritonavir, 100 mg BID for 14 days	4.03	23.9	3.44	18.9	**0.85**	**0.79**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
63	(42)	CYP3A4/5	Midazolam, 2 mg on Day 16	Ritonavir, 200 mg TID day 1, 300 mg Day 2-7, 400 mg BID days 8-15	-	10.5	-	19.05	-	**1.81**
64	(43)	CYP3A4/5	Nifedipine, 10 mg TID for 4 days, 1 dose day 5.	Cimetidine, 800 mg QD for 5 days	2.3	2.0	1.39	1.61	**0.60**	**0.81**
65	(44)	CYP3A4/5	Nifedipine, 10 mg QID for 6 days, 1 dose day 7.	Cimetidine, 200 mg TID with 400 mg at night for 7 days	2.02	1.6	1.12	1.22	**0.55**	**0.76**
66	(45)	CYP3A4/5	Nifedipine, 20 mg SD day 2 (1hr after first cimetidine dose)	Cimetidine, 200 mg TID with 400 mg at night for 3 days	-	1.31	-	1.22	-	**0.93**
67	(46)	CYP3A4/5	Nifedipine, 20 mg SD day 7	Cimetidine, 300 mg QID for 7 days	1.4	1.52	1.52	1.31	**0.85**	**0.86**
68	(47)	CYP3A4/5	Nifedipine, 20 mg SD day 5 (1hr after cimetidine)	Cimetidine, 800 mg QD for 5 days	1.65	1.77	1.5	1.67	**0.91**	**0.94**
69	(48)	CYP3A4/5	Nifedipine, 20 mg SD	Diltiazem, 60 mg 1 hour before nifedipine	-	1.33	-	1.18	-	**0.89**
70	(48)	CYP3A4/5	Nifedipine, 20 mg SD	Diltiazem, 60 mg TDS for 3 days and a final dose 1 hour before nifedipine	-	2.4	-	2.57	-	**1.07**
71	(48)	CYP3A4/5	Nifedipine, 20 mg SD	Diltiazem, 60 mg TDS for 6 days and a final dose 1 hour before nifedipine	-	2.96	-	2.73	-	**0.92**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
72	[49]	CYP3A4/5	Nifedipine, 20 mg SD	Diltiazem, 30 mg TDS for 3 days and a final dose 1 hour before nifedipine	2.01	2.2	1.39	1.79	**0.69**	**0.82**
73	[49]	CYP3A4/5	Nifedipine, 20 mg SD	Diltiazem, 90 mg TDS for 3 days and a final dose 1 hour before nifedipine	1.7	3.1	1.87	3.23	**1.1**	**1.04**
74	[50]	CYP3A4/5	Quinidine, 332 mg SD (day 4)	Verapamil, 80 mg TID for 4 days (12 doses)	-	1.47	-	2.45	**-**	**1.67**
75	[50]	CYP3A4/5	Quinidine, 332 mg SD (day 4)	Verapamil, 120 mg TID for 4 days (12 doses)	-	1.5	-	2.89	**-**	**1.93**
76	[51]	CYP3A4/5	Quinidine, 200 mg SD (day 3), (1.5 h after last Diltiazem dose)	Diltiazem, 90 mg BID for 3 days (5 doses)	1.09	1.51	1.18	1.66	**1.08**	**1.10**
77	[52]	CYP3A4/5	Quinidine, 330 mg (free base) SD on day 6	Cimetidine, 300 mg QID for 7 days	1.2	1.57	1.07	1.15	**0.89**	**0.73**
78	[53]	CYP3A4/5	Quinidine, 330 mg (free base) SD on day 4	Cimetidine, 300 mg QID for 3 days, morning dose day 4	1	1.27	1.06	1.09	**1.06**	**0.86**
79	[54]	CYP3A4/5	Quinidine, 166 mg free base, single dose, oral	Itraconazole, 100 mg, QD, 7 days, oral	1.32	2.58	1.33	2.23	**1.01**	**0.86**
80	[55]	CYP3A4/5	Quinidine, 83 mg free base, single dose, day 4	Itraconazole, 200 mg QD, oral, 4 days	1.59	2.42	1.37	2.84	**0.86**	**1.17**
81	[54]	CYP3A4/5	Quinidine, 166 mg free base, single dose, oral	Erythromycin, 250 mg, QID, 7 days, oral	1.39	1.19	1.26	2.45	**0.91**	**2.06**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
82	(56)	CYP3A4/5	Quinidine, 166 mg free base, single dose, oral, day 5	Fluvoxamine, 100 mg, QD, oral, 6 days	1.35	1.41	1.1	1.22	**0.81**	**0.87**
83	(57)	CYP3A4/5	Repaglinide, 0.25 mg on day 3 (1 h after Itraconazole)	Itraconazole, 200 mg (1st dose) 100 mg BID for 3 days (7 doses)	1.47	1.42	1.35	1.57	**0.92**	**1.11**
84	(58)	CYP3A4/5	Repaglinide, 0.25 mg SD (1h after 2nd Cyclosporine dose)	Cyclosporine, 100 mg BID (2 doses, 8 pm and 8 am)	1.71	2.44	1.53	1.68	**0.89**	**0.69**
85	(59)	CYP3A4/5	Repaglinide, 0.25 mg day 5 given 1 hour after clarithromycin	Clarithromycin, 250 mg oral every 12 h for 4 days	1.66	1.4	1.74	2.17	**1.05**	**1.55**
86	(58)	CYP3A4/5	Repaglinide, 0.25 mg, 1hr after 2nd dose of cyclosporine	Cyclosporine, 100 mg, BID for 1 day	1.71	2.44	1.53	1.68	**0.89**	**0.69**
87	(60)	CYP3A4/5	Rifabutin, 300 mg QD for 14 days	Fluconazole, 200 mg QD for 14 days	1.88	1.82	1.28	1.64	**0.68**	**0.90**
88	(61)	CYP3A4/5	Rifabutin, 300 mg QD from day 15	Fluconazole, 200 mg QD for 28 days	1.7	1.8	1.29	1.66	**0.76**	**0.92**
89	(60)	CYP3A4/5	Rifabutin, 300 mg QD for 10 days	Ritonavir, 500 mg BD for 10 days	1.5	3.0	1.7	2.62	**1.13**	**0.87**
90	(62)	CYP3A4/5	Rifabutin, 300 mg QD for 42 days	Clarithromycin, 500 mg BD from day 15	1.69	1.99	1.43	1.96	**0.85**	**0.98**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
91	(63)	CYP3A4/5	Sildenafil, 50 mg SD (2 h after Clarithromycin dose)	Clarithromycin, 500 mg SD	2.42	2.28	1.46	1.69	**0.60**	**0.74**
92	(64)	CYP3A4/5	Sildenafil, 100 mg (day 5), (1 h after 10th Erythromycin dose)	Erythromycin, 500 BID for 5 days (10 doses)	2.09	2.58	2.13	4.35	**1.02**	**1.68**
93	(65)	CYP3A4/5	Sildenafil, 100 mg SD (day 6)	Ritonavir, 300 mg BID Day 1 400 mg BID Day 2 500 mg BID Days 3-7 (14 doses)	3.89	9.9	2.8	10.08	**0.72**	**1.02**
94	(66)	CYP3A4/5	Sildenafil, 50 mg SD day 3 (2hrs after cimetidine)	Cimetidine, 800 mg QD for 4 days	1.54	1.56	1.36	1.42	**0.88**	**0.91**
95	(67)	CYP3A4/5	Simvastatin, 20 mg SD (day 15), (12 h after last Diltiazem dose)	Diltiazem, 120 mg BID for 14 days (28 doses)	3.61	4.82	3.89	5.1	**1.08**	**1.06**
96	(68)	CYP3A4/5	Simvastatin, 40 mg QD on Day 4	Amiodarone, 40 mg Days 1-4	1.79	1.76	1.53	1.64	**0.86**	**0.93**
97	(69)	CYP3A4/5	Simvastatin, 40 mg SD on Day 2	Erythromycin, 500 mg t.i.d. for 2 days	3.5	6.2	7.46	12.48	**2.13**	**2.01**
98	(69)	CYP3A4/5	Simvastatin, 40 mg SD on Day 2	Verapamil, 80mg t.i.d. for 2 days	2.6	4.6	6.5	8.32	**2.5**	**1.81**
99	(70)	CYP3A4/5	Simvastatin, 40 mg SD on Day 6. 2hrs before Ketoconazole	Ketoconazole, 400 mg QD for 10 days	7.4	12.6	3.46	8.04	**0.47**	**0.64**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
100	(71)	CYP3A4/5	Simvastatin, 40 mg QD for 8 days	Clarithromycin, 500 mg bid for 8 days	7.1	10	9.68	16.52	**1.36**	**1.65**
101	(72)	CYP3A4/5	Triazolam, 0.25 mg (day 2), (1h after 5th Diltiazem dose)	Diltiazem, 60 mg TID for 2 days (5 doses)	1.86	2.83	1.45	2.02	**0.78**	**0.71**
102	(73)	CYP3A4/5	Triazolam, 0.25 mg SD (day 4 @3pm)	Fluconazole, 100 mg QD for 4 days (@2pm)	1.25	2.1	1.43	1.88	**1.144**	**0.8952 381**
103	(73)	CYP3A4/5	Triazolam, 0.25 mg SD on day 4 (1 hour after Fluconazole)	Fluconazole, 50 mg QD for 4 days (4 doses)	1.47	1.63	1.25	1.51	**0.85**	**0.93**
104	(74)	CYP3A4/5	Triazolam, 0.25mg SD on day 4 (1 hour after Fluconazole)	Fluconazole, 100 mg QD for 4 days (4 doses)	1.4	2.05	1.43	1.97	**1.02**	**0.96**
105	(74)	CYP3A4/5	Triazolam, 0.25 mg SD on day 4 (1 hour after fluconazole)	Fluconazole, 400 mg Day 1, then 200 mg QD for 3 days (4 doses)	2.33	4.42	1.68	3.01	**0.72**	**0.68**
106	(3)	CYP3A4/5	Triazolam, 0.25 mg SD (day 3), (1 h after Ketoconazole dose)	Ketoconazole, 200 mg BID for 4 days (8 doses)	2.08	13.7	2.42	10.9	**1.17**	**0.8**
107	(75)	CYP3A4/5	Triazolam, 0.125 mg SD (day 2), (1h after 3rd Clarithromycin dose)	Clarithromycin, 500 mg given at 8 am and 4 pm Day 1 and 8 am and 5 pm on Day 2 (4 doses)	1.97	5.06	1.99	4.18	**1.01**	**0.83**
108	(76)	CYP3A4/5	Triazolam, 0.5 mg SD (Day 2)	Cimetidine, 300 mg QID for 2 days	1.39	1.32	1.18	1.22	**0.85**	**0.92**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
109	[8]	CYP3A4/5	Triazolam, 0.5 mg QD at night for 7 days	Cimetidine, 200 mg TID with 400 mg at night for 9 days	1.51	2.2	1.23	1.29	**0.81**	**0.59**
110	[77]	CYP3A4/5	Triazolam, 0.5 mg SD (1 hr after 3rd cimetidine dose)	Cimetidine, 300 mg QID (4 doses)	1.35	1.55	1.16	1.2	**0.86**	**0.77**
111	[75]	CYP3A4/5	Triazolam, 0.125 mg Day 2 at 3 pm	Erythromycin, 500 mg BID 2 days	1.77	3.65	1.67	2.77	**0.94**	**0.76**
112	[73]	CYP3A4/5	Triazolam, 0.25 mg SD Day 4 1 hour after Fluconazole	Fluconazole, 50 mg QD for 4 days	1.47	1.63	1.25	1.51	**0.85**	**0.93**
113	[73]	CYP3A4/5	Triazolam, 0.25 mg SD Day 4 1 hour after Fluconazole	Fluconazole, 200 mg QD for 4 days (day 1 loading dose of 400 mg)	2.33	4.42	1.68	3.01	**0.72**	**0.68**
114	[78]	CYP3A4/5	Zolpidem, 10 mg (8.04mg free base) SD day 4	Itraconazole (Fed capsule), 200 mg QD for 4 days	1.1	1.34	1.18	1.77	**1.07**	**1.32**
115	[79]	CYP2C9	S-Warfarin, 0.375 mg/kg SD day 7 (1hr before Fluconazole)	Fluconazole, 400 mg QD for 14 days	-	2.92	-	2.75	**-**	**0.94**
116	[80] (*1/*1 genotyped subjects)	CYP2C9	S-Warfarin, 8.75 mg SD day 14	Fluconazole, 400 mg QD for 20 days	1.11	1.86	1.07	2.56	**0.96**	**1.38**
117	[80] (simulated as	CYP2C9	S-Warfarin, 8.75 mg SD day 14	Fluconazole, 400 mg QD for 20 days	1.11	1.86	1.07	2.56	**0.96**	**1.38**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
	EM phenotype)									
118	(81)	CYP2C9	Tolbutamide, 500 mg SD (2hrs after Fluconazole)	Fluconazole, 150 mg SD	1.23	1.90	1.09	1.31	**0.89**	**0.69**
119	(81)	CYP2C9	Tolbutamide, 500 mg SD Day 8 (2hrs after fluconazole)	Fluconazole, 150 mg QD, day 1; 100 mg QD days 2 - 8	1.3	2.09	1.13	1.51	**0.87**	**0.72**
120	(82)	CYP2C9	Phenytoin, 250 mg SD day 5	Fluconazole, 400 mg QD, 6 days	-	1.33	-	1.4	**-**	**1.05**
121	*(83)*	CYP2C9	S-Warfarin, 0.375 mg/kg SD day 7 (1h before Fluconazole)	Fluconazole, 100 mg QD for 18 days	-	1.35	-	1.51	**-**	**1.12**
122	*(83)*	CYP2C9	S-Warfarin, 0.375 mg/kg SD day 7 (1h before fluconazole)	Fluconazole, 200 mg QD for 18 days	-	1.86	-	2.00	**-**	**1.08**
123	*(83)*	CYP2C9	S-Warfarin, 0.375 mg/kg SD day 7 (1h before fluconazole)	Fluconazole, 300 mg QD for 18 days	-	2.00	-	2.45	**-**	**1.23**
124	(84)	CYP2C9	Celecoxib, 200 mg SD day 7	Fluconazole, 200 mg QD for 7 days	1.68	2.34	1.41	2.24	**0.84**	**0.96**
125	(85)	CYP2C9	Tolbutamide, 500 mg SD on day 5 (8.00 am)	Fluvoxamine, 75 mg (54.98 mg free base) QD for 5 days (dosed at 8.00 pm)	-	1.25	-	1.38	**-**	**1.11**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
126	(85)	CYP2C9	Tolbutamide, 500 mg SD on day 5 (8.00 am)	Fluvoxamine, 150 mg (109.95 mg free base) QD for 5 days (dosed at 8.00 pm)	-	1.93	-	1.7	-	**0.88**
127	(86)	CYP2C9	Phenytoin, 100 mg IV SD day 7	Sulphaphenazole, 200 mg QD for 7 days	-	1.83	-	2.29	-	**1.25**
128	(87)	CYP2C9	Flurbiprofen, 100 mg SD (12.5 hrs after last dose Fluconazole)	Fluconazole, 200 mg 2 doses, 12 hours apart	1.23	1.81	1.09	1.69	**0.88**	**0.94**
129	(88)	CYP2C9	Flurbiprofen, 100 mg SD (15 hrs after last dose Fluconazole)	Fluconazole, 200 mg 2 doses, 14.5 hours apart	1.16	1.62	1.1	1.71	**0.95**	**1.05**
130	(89)	CYP2C9	Flurbiprofen, 100 mg SD (15 hrs after last dose Fluconazole)	Fluconazole, 200 mg 2 doses, 14.5 hours apart	1.47	1.97	1.09	1.68	**0.74**	**0.85**
131	(90)	CYP2C9	S-Warfarin, 0.75 mg/kg day 3	Amiodarone, 300 mg QD duration of study	-	1.27	-	1.45	-	**1.14**
132	(91)	CYP2C9	S-Warfarin, 0.75 mg/kg day 4	Amiodarone, 200 mg QD for duration of study	-	2.11	-	2.03	-	**0.96**
133	(92)	CYP2C9	Phenytoin, 5 mg/kg IV infusion (30 min) (At SS of Amiodarone)	Amiodarone, 200 mg QD for duration of study	-	1.39	-	1.39	-	**1.00**
134	(92)	CYP2C9	Phenytoin, 2 to 4 mg/kg QD for 14 days (start at SS of Amiodarone)	Amiodarone, 200 mg QD for duration of study	1.33	1.4	1.22	1.45	**0.92**	**1.03**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
135	(93)	CYP2C9	Tolbutamide, 500 mg IV day 4, 10 am	Sulphaphenazole, 500 mg BID 4 days (9 am and 9 pm), 7 doses	-	3.10	-	3.78	**-**	**1.22**
136	(94)	CYP2D6	Atomoxetine, 25 mg Day 6	Fluvoxamine, 50 mg (36.7 mg free base) QD days 1-3, 100 mg (73.3 mg free base) QD days 4-6	1.25	1.33	1.27	1.47	**1.02**	**1.10**
137	(95) (no 2D6 PMs)	CYP2D6	Atomoxetine, 25 mg Day 6	Paroxetine, 20 mg BID Days 1-2, 20 mg QD days 3-6	1.68	5.79	1.6	5.57	**0.95**	**0.96**
138	(96) (2D6 EMs)	CYP2D6	Atomoxetine, 20 mg BID from day 12 (11 doses)	Paroxetine, 20 mg QD for 17 days	3.52	6.5	3.24	5.46	**0.92**	**0.84**
139	(97)	CYP2D6	Desipramine, 50 mg on Day 6	Paroxetine, 20 mg QD for 9 days	1.79	3.76	1.82	3.67	**1.02**	**0.98**
140	(98) (EMs)	CYP2D6	Desipramine, 100 mg on Day 11 (8 am)	Paroxetine, 20 mg QD for 20 days (8 am)	2.26	6.57	1.93	6.59	**0.85**	**1.00**
141	(98) (PMs)	CYP2D6	Desipramine, 100 mg on Day 11 (8 am)	Paroxetine, 20 mg QD for 20 days (8 am)	0.91	0.92	1.0	1.0	**1.1**	**1.09**
142	(99) (EMs)	CYP2D6	Desipramine, 50 mg QD for 20 days	Par: 20 mg QD days 8-17, 30 mg QD days 18-20	4.68	5.46	5.29	6.35	**1.13**	**1.16**
143	(100)	CYP2D6	Desipramine, 50 mg (3 hours after Fluoxetine)	Fluoxetine, 60 mg Day 1	1.63	2.25	1.56	2.39	**0.96**	**1.06**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
144	[100] (MD)	CYP2D6	Desipramine, 50 mg on Day 8 (3 hours after Fluoxetine)	Fluoxetine, 60 mg QD for 8 Days	2.54	7.43	2.09	5.27	**0.82**	**0.71**
145	[101]	CYP2D6	Desipramine, 50 mg QD for 28 Days	Fluoxetine, 20 mg QD Days 8-28	3.78	4.42	3.86	4.49	**1.02**	**1.02**
146	[102]	CYP2D6	Desipramine, 50 mg on Day 5	Cinacalcet, 90 mg QD for 7 days	1.7	2.5	1.95	2.48	**1.15**	**0.99**
147	[103]	CYP2D6	Desipramine, 50 mg on Day 15	Bupropion, 15 mg QD days 1-3, 150 mg BID days 4-14, 150 mg SD Day 15	1.9	5.2	2.15	4.94	**1.13**	**0.95**
148	[104]	CYP2D6	Desipramine, 50 mg on Day 17	Ritonavir, 100 mg BID for 20 days	1.08	1.26	1.08	1.19	**1**	**0.94**
149	[105]	CYP2D6	Dextromethorphan, 30 mg SD	Quinidine, 50 mg (1 hour before dextromethorphan)	4.38	7.31	4.29	5.74	**0.98**	**0.79**
150	[106]	CYP2D6	Dextromethorphan, 30 mg SD	Quinidine, 50 mg (1 hour before dextromethorphan)	6.1	6.34	4.17	5.53	**0.68**	**0.87**
151	[107]	CYP2D6	Dextromethorphan, 30 mg on Day 12	Fluoxetine, 20 mg SD Day 1, then 60mg QD days 2-14 (1 hour before Dextromethorphan)	-	27	-	13.56	**-**	**0.5**
152	[108] (EMs)	CYP2D6	Metoprolol Tartrate, 100 mg BID on Day 7	Paroxetine, 20 mg QD for 7 days	2.2	3.43	2.7	4.27	**1.23**	**1.24**
153	[109] (EM)	CYP2D6	Metoprolol Tartrate, 100 mg on Day 7	Paroxetine, 10 mg every 12 hours for 7 days (13 doses)	2.21	6.16	2.03	4.92	**0.92**	**0.80**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
154	[110] (EMs)	CYP2D6	Metoprolol Tartrate, 200 mg on Day 4 (2 hours after Quinidine)	Quinidine, 100 mg QD for 5 days	-	4.89	-	4.59	**-**	**0.94**
155	[111] (EMs)	CYP2D6	Metoprolol Tartrate, 20mg IV infusion	Quinidine, 50 mg SD (12 hours before metoprolol)	-	2.43	-	1.48	**-**	**0.61**
156	[112]	CYP2D6	Nebivolol, 5 mg on Day 8	Paroxetine, 20 mg BID Days 1-2, 20mg QD days 3-7	2.38	6.96	3.72	8.6	**1.56**	**1.24**
157	[113]	CYP2D6	Nebivolol, 5 mg on Day 8	Bupropion, 150 mg BID days 1-3, 300 mg days 4-7	2.38	6.98	4.17	8.93	**1.75**	**1.28**
158	[114]	CYP2D6	Nebivolol, 5 mg on Day 8	Fluvoxamine, 50 mg QD days 1-3, 100 mg QD days 3-7	1.32	1.57	1.66	1.61	**1.26**	**1.03**
159	[115]	CYP2D6	Nebivolol, 10 mg QD days 1-20	Fluoxetine, 20 mg QD days 1-20	2.39	6.92	3.97	7.46	**1.66**	**1.08**
160	[116] (EMs)	CYP2D6	Tolterodine, 1.368 mg BID days 22-24 (5 doses)	Fluoxetine, 20 mg QD for 24 days	3.57	4.87	3.76	6.7	**1.05**	**1.37**
161	[116] (PMs)	CYP2D6	Tolterodine, 1.368 mg BID days 22-24 (5 doses)	Fluoxetine, 20 mg QD for 24 days	1.36	1.24	1.05	1.12	**0.77**	**0.90**
162	[94]	CYP2D6	Atomoxetine, 25 mg on day 6	Fluvoxamine, 50 mg (36.7 mg free base) QD days 1-3, 100 mg (73.3 mg free base) QD days 4-6	1.25	1.33	1.25	1.43	**1.00**	**1.07**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
163	(97)	CYP2D6	Desipramine, 50 mg on day 6	Paroxetine, 20 mg QD for 9 days	1.90	5.19	1.76	4.62	**0.93**	**0.89**
164	(117)	CYP2C8	Repaglinide, Oral 0.25 mg on day 3 at 9 AM	Trimethoprim, Oral 160 mg every 12 hours for 3 days at 8 AM and 8 PM	1.4	1.59	1.24	1.37	**0.89**	**0.86**
165	(118)	CYP2C8	Repaglinide, Oral 0.25 mg on day 3 (1hr after Gemfibrozil dosing)	Gemfibrozil, Oral 600 mg BID for 3 days	2.63	6.57	2.98	6.44	**1.13**	**0.98**
166	(119)	CYP2C8	Repaglinide, Oral 0.25 mg on day 3 (concomitant after Gemfibrozil dosing)	Gemfibrozil, Oral 600 mg BID for 3 days	2.2	6.1	2.42	5.59	**1.10**	**0.92**
167	(120) OATP1B1 ET subjects	CYP2C8	Repaglinide, Oral 0.25 mg on day 3 (1hr after Gemfibrozil dosing)	Gemfibrozil, Oral 600 mg BID for 3 days	2.6	7.0	3.03	6.61	**1.17**	**0.94**
168	(120) OATP1B1 IT subjects	CYP2C8	Repaglinide, Oral 0.25 mg on day 3 (1hr after Gemfibrozil dosing)	Gemfibrozil, Oral 600 mg BID for 3 days	2.21	6.14	2.75	6.25	**1.24**	**1.02**
169	(120) OATP1B1 PT subjects	CYP2C8	Repaglinide, Oral 0.25 mg on day 3 (1hr after Gemfibrozil dosing)	Gemfibrozil, Oral 600 mg BID for 3 days	1.88	5.51	2.21	5.02	**1.18**	**0.91**
170	(121)	CYP2C8	Repaglinide, Oral 0.25 mg on day 5 (1hr after Gemfibrozil dosing)	Gemfibrozil, Oral 600 mg BID for 5 days	2.05	7.04	2.97	6.51	**1.45**	**0.92**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
171	(57)	CYP2C8	Repaglinide, Oral 0.25 mg on day 3 (1 hr after Gemfibrozil)	Gemfibrozil, Oral 600 mg BID for 3 days	2.39	5.89	2.94	6.35	**1.23**	**1.08**
172	(122)	CYP2C8	Rosiglitazone, Oral 4 mg on day 3 at 9 AM	Trimethoprim, Oral 160 mg every 12 hours for 4 days (at 8 AM and 8 PM on day 1, 2, 1834; at 8 AM and 9 PM on day 3)	1.14	1.37	1.08	1.22	**0.95**	**1.02**
173	(123)	CYP2C8	Rosiglitazone, Oral 8 mg on day 4 at 8 AM	Trimethoprim, Oral 200 mg every 12 hours for 4 days (at 7:30 AM and 7:30 PM)	0.88	1.31	1.1	1.48	**1.25**	**1.13**
174	(124)	CYP2C8	Rosiglitazone, Oral 4 mg at 9 AM on day 3	Gemfibrozil, Oral 600 mg every 12 hours at 8 AM and 8 PM for 7 doses	1.22	2.29	1.17	2.38	**0.96**	**1.04**
175	(125)	CYP2C8	Repaglinide, Oral 0.25 mg on day 5 (1hr after Gemfibrozil dosing)	Gemfibrozil, Oral 100 mg BID for 5 days (9 doses)	1.86	5.57	1.79	2.51	**0.96**	**0.45**
176	(125)	CYP2C8	Repaglinide, Oral 0.25 mg on day 5 (1hr after Gemfibrozil dosing)	Gemfibrozil, Oral 30 mg BID for 5 days (9 doses)	1.45	3.40	1.31	1.50	**0.90**	**0.44**
177	(119)	CYP2C8	Repaglinide, Oral 0.25 mg on day 3 (3 h after Gemfibrozil dosing)	Gemfibrozil, Oral 600 mg BID for 3 days (5 doses)	1.95	5.79	2.88	5.26	**1.48**	**0.91**
178	(119)	CYP2C8	Repaglinide, Oral 0.25 mg on day 3 (6 h after Gemfibrozil dosing)	Gemfibrozil, Oral 600 mg BID for 3 days (5 doses)	2.24	5.73	2.15	3.21	**0.96**	**0.56**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
179	(126)	CYP2C8	Repaglinide, Oral 0.25 mg on day 3 (12 h after Gemfibrozil dosing)	Gemfibrozil, Oral 600 mg BID for 3 days (5 doses)	2.19	4.77	1.50	1.88	**0.69**	**0.39**
180	(129)	CYP1A2	Caffeine, 3 mg/kg SD (Day 4 @9:00 AM)	Ciprofloxacin, 100 mg BID for 4 days (7 doses)	1.07	1.17	1.12	1.26	**1.05**	**1.08**
181	(129)	CYP1A2	Caffeine, 3 mg/kg SD (Day 4)	Ciprofloxacin, 250 mg BID for 4 days (7 doses)	1.09	1.57	1.18	1.49	**1.08**	**0.95**
182	(129)	CYP1A2	Caffeine, 3 mg/kg SD (Day 4)	Ciprofloxacin, 500 mg BID for 3 days (6 doses) + 500 mg morning dose	1.17	1.58	1.23	1.74	**1.05**	**1.10**
183	(130)	CYP1A2	Caffeine, 100 mg TID for 3 days (7 doses)	Ciprofloxacin, 500 mg BID for 3 days (5 doses)	1.45	1.8	1.55	1.93	**1.07**	**1.07**
184	(130)	CYP1A2	Caffeine, 100 mg TID for 3 days (7 doses)	Ciprofloxacin, 500 mg BID for 3 days (5 doses)	1.7	2.03	1.54	1.98	**0.91**	**0.98**
185	(131)	CYP1A2	Caffeine, 183 mg QD for 5 days	Ciprofloxacin, 750 mg BID for 7 days (14 doses)	1.14	2.45	1.46	2.4	**1.28**	**0.98**
186	(132)	CYP1A2	Caffeine, 250 mg SD (Day 2)	Fluvoxamine, 100 mg (73.3 mg free base) BID for 2 days (4 doses)	1.4	13.7	1.34	12.31	**0.96**	**0.95**
187	(133) CYP2D6 EMs	CYP1A2	Caffeine, 100 mg SD (Day 6)	Fluvoxamine, 25 mg (18.3 mg free base) BID for 6 days (12 doses)	2.9	6.14	1.34	4.5	**0.46**	**0.73**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
188	(134)	CYP1A2	Theophylline, 250 mg SD (Day 8 @8 AM)	Fluvoxamine, 25 mg (18.3 mg free base) QD for 9 days (9 doses)	1.01	1.44	1.07	2.42	**1.06**	**1.68**
189	(134)	CYP1A2	Theophylline, 250 mg SD (Day 8 @8 AM)	Fluvoxamine, 50 mg (36.7 mg free base) QD on day 1, 75 mg (55 mg free base) QD days 2-9 (dosed at 4 PM)	1.2	2.03	1.08	2.87	**0.90**	**1.41**
190	(135)	CYP1A2	Theophylline, 4 mg/kg SD (Day 6)	Fluvoxamine, 50 mg QD days 1-2, 50 mg (36.7 mg free base) BID days 3-7	1.11	2.66	1.08	4.03	**0.97**	**1.52**
191	(136)	CYP1A2	Theophylline, 3.4 mg/kg SD (Day 4 @9.00 AM)	Ciprofloxacin, 500 mg BID for 5 days (Day 1 @9.00 PM to Day 5 @9.00 PM) (9 doses)	-	1.24	-	1.57	**-**	**1.27**
192	(135)	CYP1A2	Theophylline, 5 mg/kg SD IV infusion (30 minutes) (Day 7 @9 AM)	Ciprofloxacin, 500 mg BID for 7 days (Day 1 @9 AM to Day 7 @9 AM) (13 doses)	1.1	1.34	1.01	1.3	**0.92**	**0.97**
193	(136)	CYP1A2	Theophylline, 125 mg oral dose TID for 7 days (Day 1 @8 AM to Day 7 @8 AM)	Ciprofloxacin, 500 mg BID for 7 days (Day 1 @8 AM to Day 7 @8 AM)	-	1.35	-	1.59	**-**	**1.18**
194	(137)	CYP1A2	Theophylline, 5 mg/kg SD IV infusion (30 minutes) (Day 5 @9 AM)	Ciprofloxacin, 500 mg BID for 8 days (16 doses)	-	1.5	-	1.56	**-**	**1.04**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
195	(137)	CYP1A2	Theophylline, 5 mg/kg SD IV infusion (30 minutes) (Day 5 @9 AM)	Ciprofloxacin, 500 mg BID for 8 days (16 doses)	-	1.49	-	1.55	**-**	**1.04**
196	(138)	CYP1A2	Theophylline, 5 mg/kg SD IV infusion (30 minutes) (Day 5 @7 AM)	Ciprofloxacin, 500 mg BID for 7 days (Day 1 @7 AM to Day 7 @7 PM) (14 doses)	-	1.48	-	1.51	**-**	**1.02**
197	(139)	CYP1A2	Caffeine, 100 mg SD (Day 2 @9 AM)	Ciprofloxacin, 750 mg BID for 2 days (3 doses)	1.1	1.59	1.26	1.93	**1.15**	**1.21**
198	(140)	CYP1A2	Tizanidine, 4 mg SD (Day 4, 1h after Fluvoxamine)	Fluvoxamine, 100 mg (73.3 mg free base) QD for 4 days	12.1	32.7	9.85	32.37	**0.81**	**0.99**
199	(141)	CYP1A2	Tizanidine, 4 mg SD (Day 3, 1h after morning Ciprofloxacin dose)	Ciprofloxacin, 500 mg BID for 3 days (6 doses)	6.83	9.74	3.12	3.36	**0.46**	**0.34**
200	(142)	CYP2C19	S-Mephenytoin, 100 mg SD on day 9 (8 AM)	Fluvoxamine, 37.5 mg (27.5 mg free base) QD for 11 days (dosed at 4 PM)	2.12	4.64	2.15	5.36	**1.01**	**1.16**
201	(142)	CYP2C19	S-Mephenytoin, 100 mg SD on day 9 (8 AM)	Fluvoxamine, 62.5 mg (45.8mg free base) QD for 11 days (dosed at 4 PM)	2.4	6.7	2.45	8.14	**1.02**	**1.21**
202	(142)	CYP2C19	S-Mephenytoin, 100 mg SD on day 9 (8 AM)	Fluvoxamine, 50 mg (36.7mg free base) QD (days 1-2), 87.5 mg (64.1 mg free base) QD (days 3-11) (dosed at 4 PM)	2.42	9.89	2.64	10.70	**1.09**	**1.08**

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio
203	(127)	CYP2C19	Omeprazole, 20 mg SD day7	Fluvoxamine, 25 mg (18.3 mg free base) BID for 7 days		5.26	2.79	4.86		**0.92**
204	(106)	CYP2C19	Omeprazole, 20 mg SD day 12 (1 h after Fluoxetine)	Fluoxetine, 20 mg SD day 1, 60 mg QD days 2-14	3.79	7.1	2.49	6.3	**0.66**	**0.89**
205	(99)	CYP2C19	Imipramine, 44.26 mg SD (3hrs after Fluoxetine)	Fluoxetine, 60 mg SD	1.23	1.89	1.38	1.75	**1.12**	**0.93**
206	(99)	CYP2C19	Imipramine, 44.26 mg SD on day 8 (3hrs after Fluoxetine)	Fluoxetine, 60 mg QD for 8 days	1.75	3.33	1.93	3.48	**1.10**	**1.05**
207	(139)	CYP2C19	Omeprazole, 20 mg SD (on day 8) 1h after Ticlopidine	Ticlopidine, 200 mg ticlopidine HCL (175.65 mg free base) once a day at 8 AM (8 doses)	2.99	6.22	2.22	5.2	**0.74**	**0.84**
208	(140)	CYP2C19	Omeprazole, 40 mg SD on day 7	Ticlopidine, 100 mg of ticlopidine HCL (87.83 mg free base) TID (19 doses)	2.11	2.4	2.42	4.23	**1.15**	**1.77**
209	(127)	CYP2C19	Omeprazole, 20 mg SD day7	Fluvoxamine, 25 mg (18.3 mg free base) BID for 7 days	-	5.46	-	6.27	**-**	**1.15**
210	(127)	CYP2C19	Omeprazole, 20 mg SD day7	Fluvoxamine, 25 mg (18.3 mg free base) BID for 7 days	-	5.47	-	4.65	**-**	**0.85**

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14.Appendix 5.

Published Analysis – Mechanism/Enzyme level data

Data from the original published analysis based on enzymes and inhibitory mechanism are presented below.[12] The prediction accuracy of the updated (n=210) *versus* original dataset (n=201) were similar; AFE values were 0.92 *versus* 0.94 for competitive inhibition and 1.03 *versus* 0.99 for MBI, respectively.

Predicted *versus* observed changes in AUC and C_{max} across each of the CYP enzymes investigated are shown in Figure A3 for competitive inhibition (n=123 DDIs) and in Figure A4 for mechanism-based inhibition (n=78 DDIs).

Clinical DDIs using competitive inhibitors were investigated for a total of 123 studies for CYP1A2 (20 studies), CYP2C8 (4 studies), CYP2C9 (16 studies), CYP2C19 (4 studies), CYP2D6 (17 studies) and CYP3A4/5 (62 studies). The overall prediction accuracy was good with a bias of 0.91 and precision of 1.20 for the C_{max} ratio and values of 0.92 and 1.19, respectively, for the AUC ratio.

Across the 123 DDIs investigated with competitive inhibitors, 10% fell outside the 1.5-fold of the observed C_{max} ratio with only 3/125 falling outside 2-fold from the observed C_{max} ratio. Prediction of the AUC ratio was comparable with 8% falling outside 1.5-fold of the predicted AUC ratio and only 1 DDI investigated falling outside of 2-fold of the observed AUC ratio.

Clinical DDIs involving MBI were investigated for CYP2C8 (8 studies), CYP2C9 (4 studies), CYP2C19 (5 studies), CYP2D6 (9 studies) and CYP3A4/5 (52 studies). The prediction accuracy was good across all CYPs investigated with a bias of 1.03 for both C_{max} and AUC ratios and a precision of 1.20 and 1.26 for C_{max} and AUC ratios, respectively.

For the C_{max} ratio, 6% fell outside of 1.5-fold of the observed C_{max} from the clinical studies, with 2 out of the 62 studies falling outside of 2-fold for interactions using simvastatin as a substrate of CYP3A4/5. Prediction of AUC ratios had a slightly higher number of studies falling 1.5-fold outside of the observed AUC ratio with 23% of the DDIs investigated not meeting these criteria, however, only 3 predictions fell outside 2-fold of the observed AUC ratio for omeprazole (CYP2C19 substrate), quinidine and simvastatin (CYP3A4 substrates).

Data from the original analysis based on enzymes and substrates are presented below for C_{max} ratios (Figure A5) and AUC ratios (Figure A6).[12]

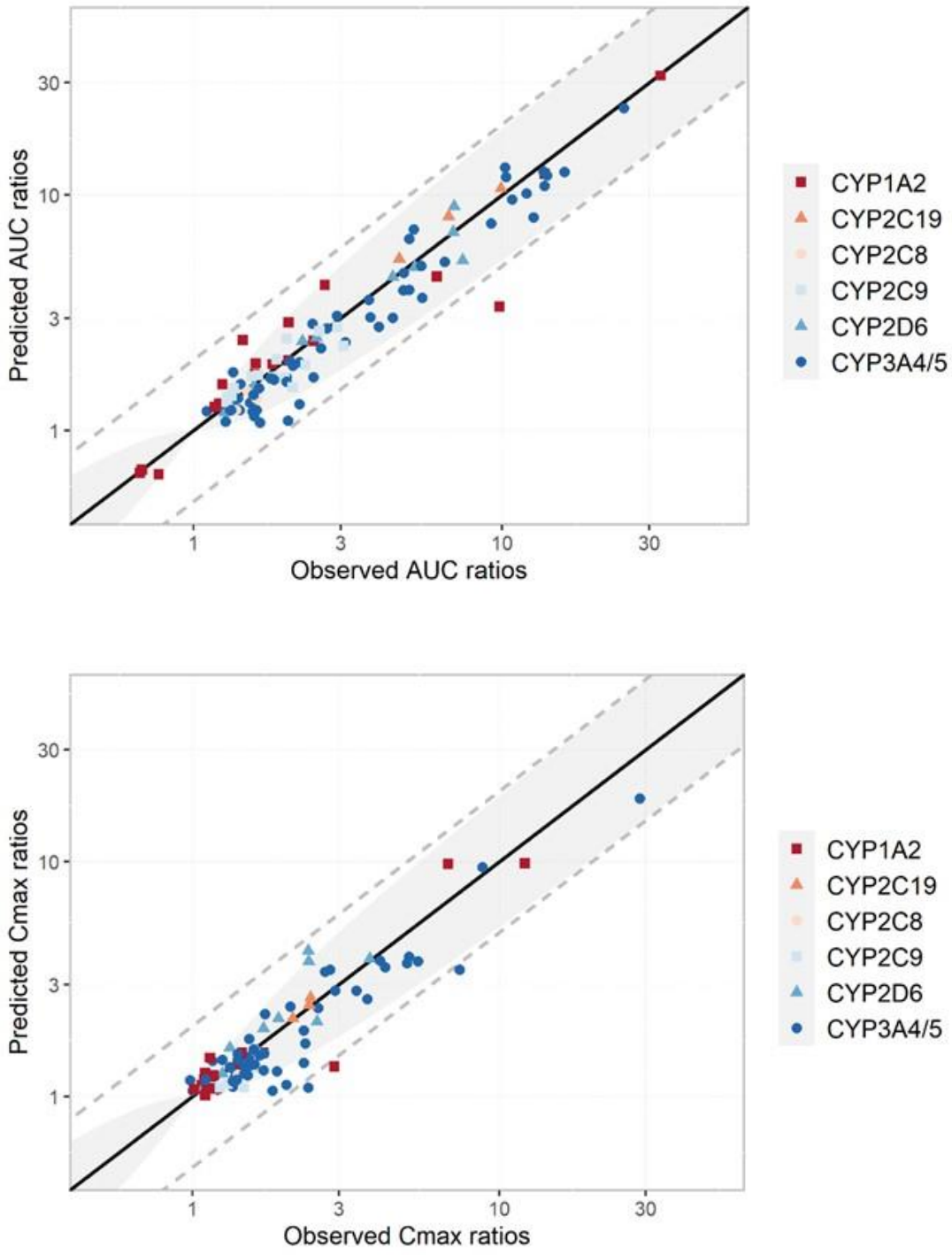

Figure A3. Predicted *versus* observed DDIs involving competitive inhibition

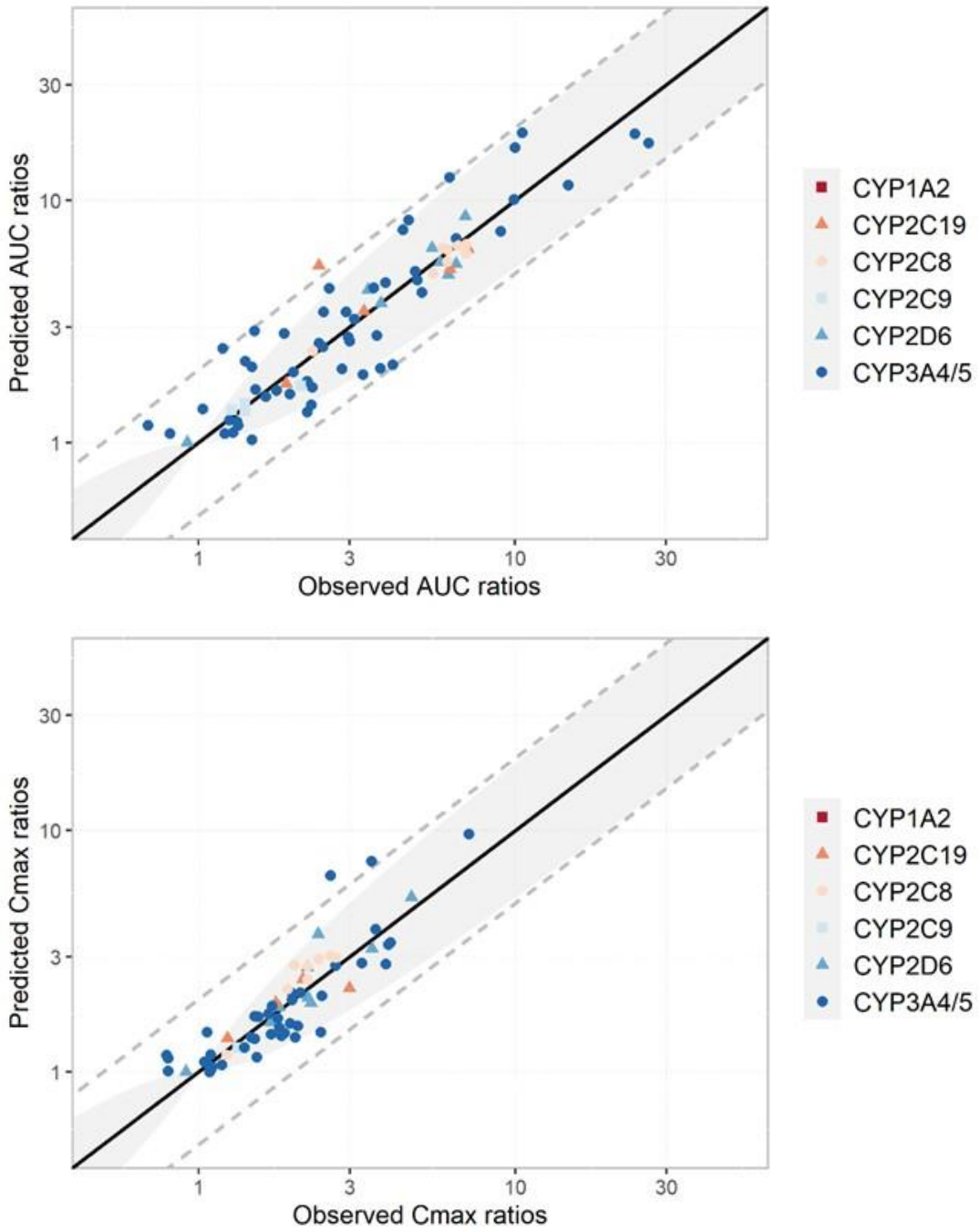

Figure A4. Predicted *versus* observed DDIs involving mechanism-based inhibition

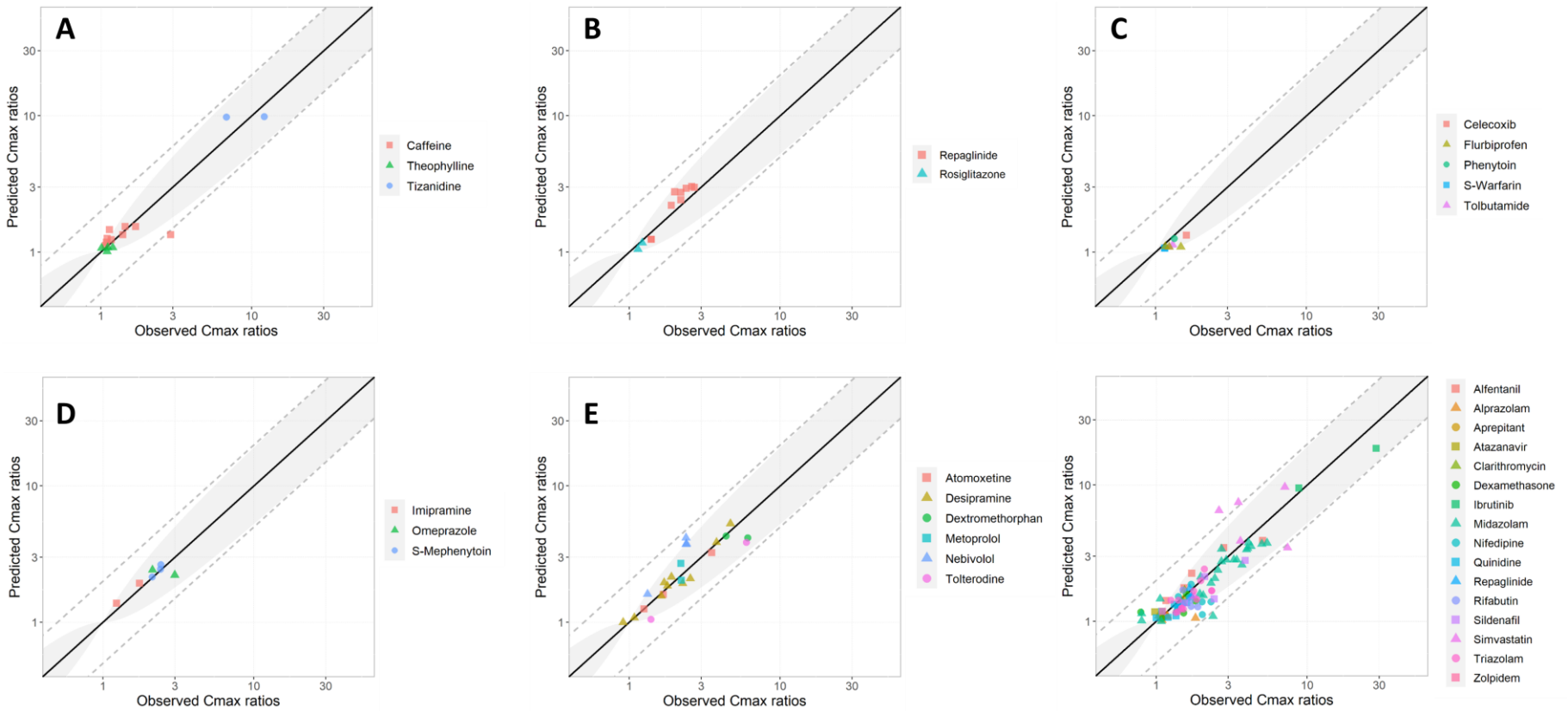

Figure A5. Predicted and observed C_{max} ratios for the qualification of CYP1A2 (A), CYP2C8 (B), CYP2C9 (C), CYP2C19 (D), CYP2D6 (E) and CYP3A4/5 (F) mediated competitive and mechanism based inhibition using the Simcyp Simulator (V19 R1).

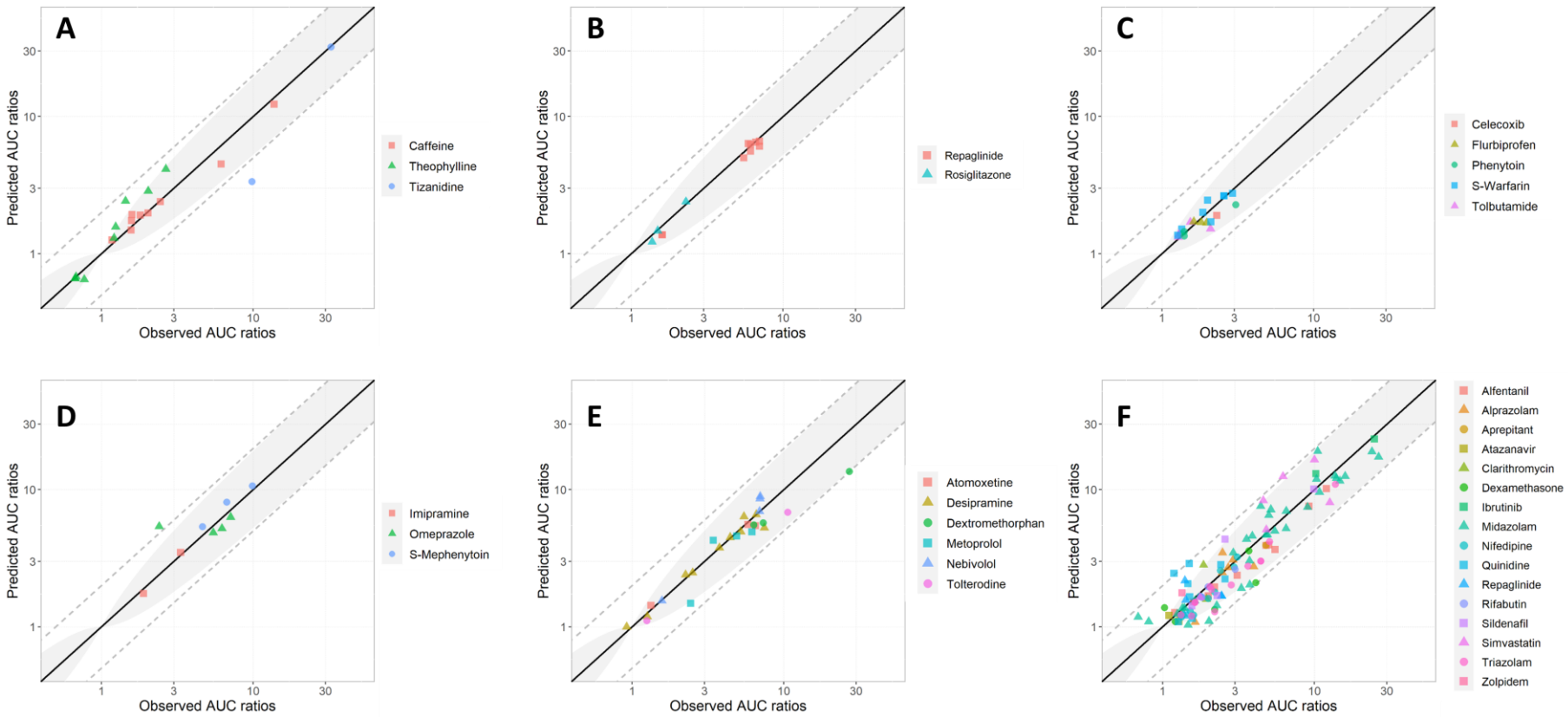

Figure A6. Predicted and observed AUC ratios for the qualification of CYP1A2 (A), CYP2C8 (B), CYP2C9 (C), CYP2C19 (D), CYP2D6 (E) and CYP3A4/5 (F) mediated competitive and mechanism based inhibition using the Simcyp Simulator (V19 R1).

15. Appendix 6.

Compound file comparison – V19/V20/V21

Two sets of comparisons are typically performed for version-to-version comparisons.

Compound files developed in a new version e.g. V20 files in the V20 simulator would be compared against V20 files in the V19 simulator – this comparison gives an indication of the impact of the changes in compound file parameters.

In addition, V20 files in the V20 simulator would be compared against V19 files in the V19 simulator. This comparison would reflect changes in system parameters as well as changes in compound file parameters.

The former has been provided for V19/V20 and the latter for V20/V21. The changes in compound file parameters which are shown in Appendix 7 do not lead to significant differences in PK between versions as can be seen by the graphs shown in the attachments below.

V20R1_V21R1_VersionComparison_64bi

V19R1_V20R1_VersionComparison_64bi

16.Appendix 7.

Version Comparisons – V19/V20/V21

Changes to input parameters were made for some compound files in going from V19 to V20 to V21 of the Simcyp Simulator. These are indicated below. The impact of these changes, which is minimal in terms of the predicted PK, are indicated in Appendix 6, where correlations of simulations for each compound are shown for V19 *versus* V20 *versus* V21.

Changes in the V20 input data for inhibitors and substrates used in the CYP-qualification in Simcyp V19:

Compound – Inhibitor file	**Parameter**	**V19**	**V20**	**Comments**
Amiodarone				
Aprepitant				
Atazanavir				
Bupropion				
Cimetidine				
Cinacalcet	Released in V20			
Ciprofloxacin				
Clarithromycin				
Cyclosporine				
Desmethyl-Diltiazem				
Diltiazem				
Erythromycin - EC	CYP3A4 K_i (μM)	82	32.8	Refined based on Meta-Analysis
	CYP3A Kapp (μM)	23.2	17.64	
	CYP3A4 K_{inact} (1/h)	2.25	0.8	
Erythromycin	fa	1	0.60	Where Erythromycin is not dosed as EC formulation alternative file can be used with refined absorption parameters
	Ka (1/h)	3.58	0.52	
Fluconazole				
Fluoxetine				
Fluvoxamine				
Gemfibrozil				
Gemfibrozil 1-O-β Glucuronide				
Itraconazole				

Ketoconazole				
Mono-desethyl Amiodarone				
Nor-Fluoxetine				
Norverapamil				
OH-Bupropion				
Paroxetine				
Quinidine				
Ritonavir	fa	-	0.5	Option to select FO file
	Ka (1/h)	-	0.45	Option to select FO file, optimised to recover profile
	fu_{gut}	-	0.015	Same as fup
Sulphaphenazole				
Ticlopidine				
Trimethoprim				
Verapamil				

Compound – Substrate file	**Parameter**	**V19**	**V20**	**Comments**
Alfentanil				
Alprazolam				
Atazanavir				
Atomoxetine		SV Atomoxetine	SV Atomoxetine	V21 2D6 Vmax increased due to phenotype changes
Caffeine				
Clarithromycin				
Desipramine				
Dexamethasone	Released in V20			
Dextromethorphan				
Flurbiprofen	Released in V21			
Ibrutinib	Released in V21			
Imipramine	Ka	0.45	0.8	Optimised to capture clinical profiles
	T_{max}	0.45	0.8	Revised to capture T_{max}
	V_{ss} CV (%)	30	20	Revised to capture variability
	2-OH CYP1A2 V_{max} (pmol/min/pmol)	2.6	1.6	Elimination parameters were determined using a retrograde

	2-OH CYP2C19 V_{max} (pmol/min/pmol)	56.8	237.2	approach and then refined based on fm data available for formation of desipramine. The retrograde CL_{int} was then used to back calculate V_{max} values using *in vitro* Km values.
	2-OH CYP2D6 V_{max} (pmol/min/pmol)	22.6	5.6	
	N-Desmethyl CYP1A2 V_{max} (pmol/min/pmol)	16.9	105.8	
	N-Desmethyl CYP2C19 V_{max} (pmol/min/pmol)	119.2	175	
	N-Desmethyl CYP2D6 V_{max} (pmol/min/pmol)	13.3	204.8	
	UGT1A4 V_{max} (pmol/min/mg)	292.5	136.78	
Metoprolol				
Midazolam				
Nebivolol	Released in V20			
Nifedipine				
Omeprazole				
Phenytoin				
Quinidine				
Repaglinide				
Rifabutin				
Rosiglitazone				
Sildenafil				
Simvastatin				
S-Mephenytoin				
S-Warfarin				
Theophylline				
Tizanidine	Not released so far			
Tolbutamide				
Tolterodine				
Triazolam				
Zolpidem				

Summary of changes to existing compound files in Version 20

Compound	Parameter	Value		Comments
		V19.1	V20	
SV-Ritonavir	fa	-	0.5	Option to select FO file
	Ka (1/h)	-	0.45	Option to select FO file, optimised to recover profile

	fu_{gut}	-	0.015	Same as fup
SV-Imipramine	ka	0.45	0.8	Optimised to capture clinical profiles
	T_{max}	0.45	0.8	Revised to capture T_{max}
	V_{ss} CV (%)	30	20	Revised to capture variability
	2-OH CYP1A2 V_{max} (pmol/min/pmol)	2.6	1.6	Elimination parameters were determined using a retrograde approach and then refined based on fm data available for formation of desipramine. The retrograde CL_{int} was then used to back calculate V_{max} values using *in vitro* Km values.
	2-OH CYP2C19 V_{max} (pmol/min/pmol)	56.8	237.2	
	2-OH CYP2D6 V_{max} (pmol/min/pmol)	22.6	5.6	
	N-Desmethyl CYP1A2 V_{max} (pmol/min/pmol)	16.9	105.8	
	N-Desmethyl CYP2C19 V_{max} (pmol/min/pmol)	119.2	175	
	N-Desmethyl CYP2D6 V_{max} (pmol/min/pmol)	13.3	204.8	
	UGT1A4 V_{max} (pmol/min/mg)	292.5	136.78	
SV-Erythromycin-EC	CYP3A4 K_i (µM)	82	32.8	Refined based on Meta-Analysis
	CYP3A Kapp (µM)	23.2	17.64	
	CYP3A4 K_{inact} (1/h)	2.25	0.8	
SV-Erythromycin	fa	1	0.60	Where Erythromycin is not dosed as EC formulation alternative file can be used with refined absorption parameters
	Ka (1/h)	3.58	0.52	

Summary of changes to existing compound files in Version 21

Compound	Parameter	Value		Comments
		V20	V21	
SV-Itraconazole (Fasted Soltn and Fed Capsule)	Intestinal P-gp Ki (µM)	-	0.0939	Ki scaled from *in vitro* data
	Liver P-gp Ki (µM)	-	0.0939	Ki scaled from *in vitro* data
SV- OH-Itraconazole	Intestinal P-gp Ki (µM)	-	0.0939	Ki scaled from *in vitro* data
	Liver P-gp Ki (µM)	-	0.0939	Ki scaled from *in vitro* data
SV-Trimethoprim	Kidney OCT2 Ki (µM)	6.97	56.0	Revised to capture DDI with Metformin after updated to EGD model
	Kidney MATE Ki (µM)	0.32	15.0	
SV-3-MethoxyMorphinian	V_{ss} (L/kg)	14.3	5.46	Updated to predicted V_{ss} using Method 3 to match approach used for parent
SV-Atomoxetine	CYP2D6 V_{max} (pmol/min/mg)	476.51	857.7	Updated to reflect changes in population with addition of IM phenotype
SV-Dextromethorphan	File name change	-	-	Updated to indicate that file should be used with peripheral sampling
	Ka (1/h)	2.6	0.45	Updated for full PBPK
	Distribution	Min	Full	Updated to full PBPK

	V_{ss}	14.3	17.95	Predicted using Method 3 & Olive Oil partition coefficient
	CYP2D6 CL_{int} O-demethylation (µl/min/mg)	250.85	678	Updated to reflect changes in population with addition of IM phenotype
	CYP2D6 CL_{int} N-demethylation (µl/min/mg)	2.15	6.08	
SV-Efavirenz	CYP1A2 CL_{int} (µl/min/pmol)	0.03	0.02028	CL_{int} was refitted using the updated populations with CYP genotype and phenotype frequencies
	CYP3A4 CL_{int} (µl/min/pmol)	0.01	0.00775	
	CYP2B6 CL_{int} (µl/min/pmol)	1.36	1.024	
	CYP2A6 CL_{int} (µl/min/pmol)	0.47	0.2387	
	Add HLM CL_{int} (µl/min/mg)	0.694	2.39	
Sim-Bufuralol	File name	Sim	SV	Updated to reflect changes in population with addition of IM phenotype
	CYP2D6 V_{max} 1-OH (pmol/min/pmol)	27.7	45.09	
	CYP2D6 V_{max} 6-OH (pmol/min/pmol)	1.5	2.44	
SV-Fluvoxamine	CYP2C19 Ki (µM)	0.006	0.0087	Updated to reflect changes in abundance and frequency of CYP2C19 in population
SV-Bupropion_SR	CYP2B6 CL_{int} (µl/min/pmol)	9.1	7.24	Updated to reflect changes in abundance and frequency of CYP2B6 in population
	CYP3A4 CL_{int} (µl/min/pmol)	0.041	0.036	
	CYP2C19 CL_{int} (µl/min/pmol)	0.406	1.565	
	CYP2C19 Pathway	OH	Pathway 2	
	Add HLM CL_{int} (µl/min/mg)	105.6	80.8	
SV-Nebivolol	CYP2D6 CL_{int} (µl/min/pmol)	433.6	607	Updated to reflect changes in population with addition of IM phenotype
SV-S-Mephenytoin	CYP2C19 CL_{int} (µl/min/pmol)	12.16	9.10	Updated to reflect changes in abundance and frequency of CYP2C19 in population
SV-Atorvastatin	rUGT Scalar – Liver	1	0.250	Updated to reflect changes in abundance and frequency of UGT1A3 in population
	rUGT Scalar – Intestine	1	0.250	
	rUGT Scalar - Kidney	1	0.250	