Qualification of the Simcyp platform for CYP-mediated drug-drug interactions: a Certara perspective

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Qualification Opinion for CYP-mediated DDIs

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion for Simcyp Simulator

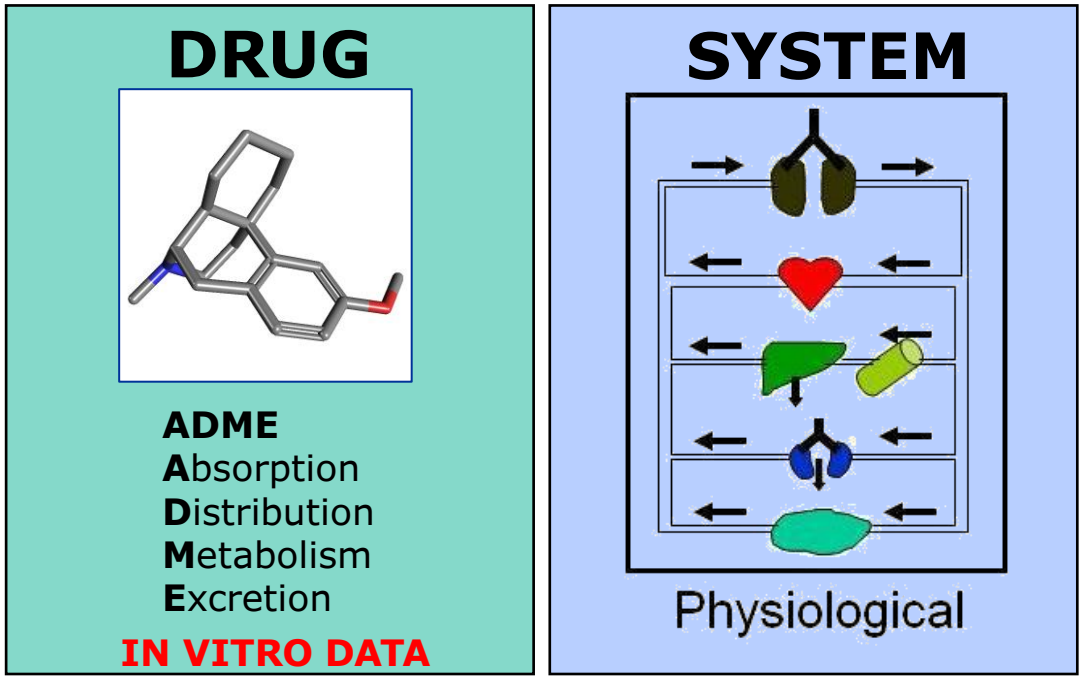
Draft agreed by Scientific Advice Working Party (SAWP)	10 April 2025
Adopted by CHMP for release for consultation	25 April 2025[1]
Start of public consultation	8 May 2025[2]
End of consultation (deadline for comments)	19 June 2025
Adoption by CHMP	24 July 2025

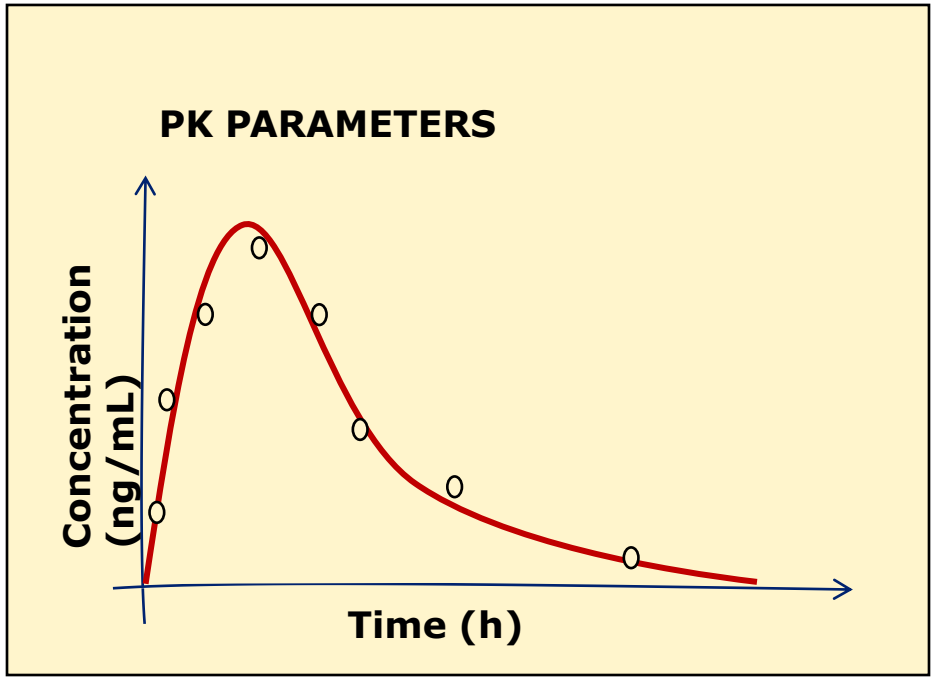
- Discussions started in 2022
- Initial submission in December 2022

Key Reflections on the Qualification Process

- Call to action for EMA to engage a team of PBPK assessors to establish common practices
- 25 years of work were reviewed - including compound files, practices, documentation – wide ranging comments
- Important to establish appropriate contexts of use
- A collaborative process especially in the latter stages
- Application of the PBPK analysis findings to the review process itself were an important part of discussions
- Pharmacometricians were actively involved in discussions especially on how to assess variability/uncertainty/bias for PBPK models

PBPK Models – Important to Review the Building Blocks





TRIAL DESIGN

NOTE: An important consideration of the Qualification Opinion.

Contexts of Use: 1-3

1. The Simcyp Simulator (V19 R1) can be used to predict the effects of weak and moderate CYP inhibitors on the exposure of a drug administered **orally** under **fasted** conditions or **intravenously** in **healthy subjects** when a clinical study with a strong CYP inhibitor has been conducted (and used to verify the fmCYP).

2. 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 administered **orally** under **fasted** conditions or **intravenously** in **healthy subjects** when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the competitive inhibition effect in vivo).

3. 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 administered **orally** under **fasted** conditions or **intravenously** in **healthy subjects** when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the MBI effect in vivo).

Context of Use: 4

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.

NOTE: A typical scenario in early development where inhibition parameters and PK data are available for drug to determine whether a clinical DDI studies needs to be performed.

Appropriate Range for Sensitivity Analysis on Ki

UOW DIDB

Paroxetine	Ki range before fu_{mic} correction	Ki range after fu_{mic} correction
Min [µM]	0.065	0.01105
Max [µM]	1.4	0.126
fold	21.54	11.4

- *In vitro* derived Ki values should always be corrected for NSMB – Ki,u.
- A positive control is typically included – Ki,u values should be determined.
- Compared against the Ki,u values of positive control if available in Simcyp Simulator V19.
- Scalar can be derived and applied to the Ki,u for the new drug.
- Thus, initial simulations can be run using the *in vitro* Ki,u value and the updated value after application of the scalar.

7.6.1.2 CYP Enzymes Inhibitors/inducers for In Vitro Studies

The enzyme inhibitors and inducers are used to phenotype individual CYP enzymes involved in the drug candidate metabolism *in vitro*. In general, the inhibitors/inducers should be selective at the concentration used. The following tables are provided to help sponsors design *in vitro* studies and to evaluate the interaction potential (Tables 5-7). These tables are not exhaustive, and sponsors can use other inhibitors/inducers with appropriate justification.

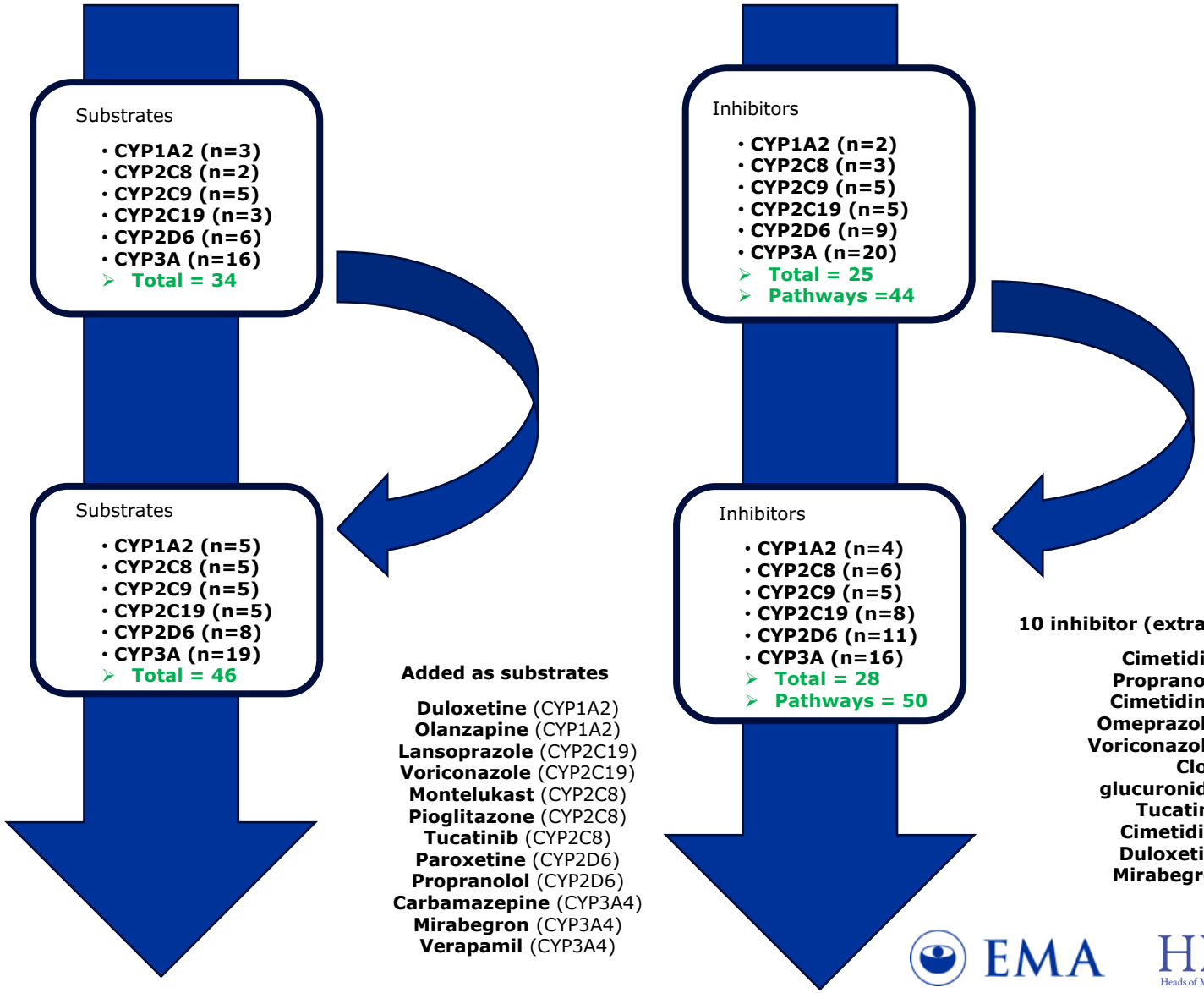
Table 5: Examples of inhibitors for CYP enzymes (*in vitro* studies)

CYP Enzyme	Inhibitor
CYP1A2	α-Naphthoflavone, Furafylline*
CYP2B6	Clopidogrel*, Ticlopidine*, Thiotepa*
CYP2C8	Gemfibrozil glucuronide*, Montelukast, Phenelzine*
CYP2C9	Sulfaphenazole, Tienilic acid*
CYP2C19	Loratadine, Ticlopidine*
CYP2D6	Paroxetine*, Quinidine
CYP3A	Azamulin*, Itraconazole, Ketoconazole, Troleandomycin*

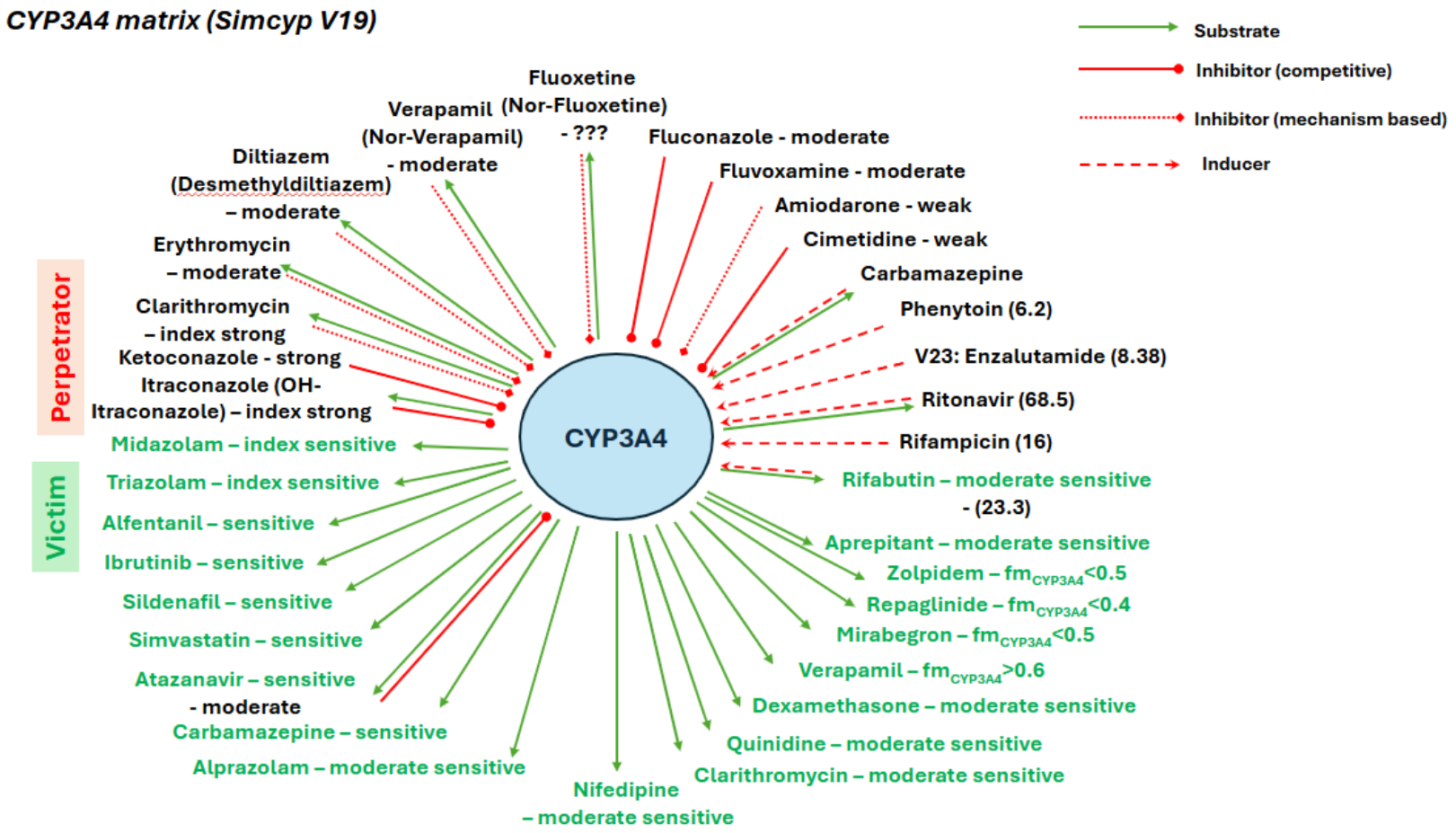
** Designated as time dependent inhibitor. When used, those inhibitors should be pre-incubated with the experimental system.*

Representative Qualification Matrix

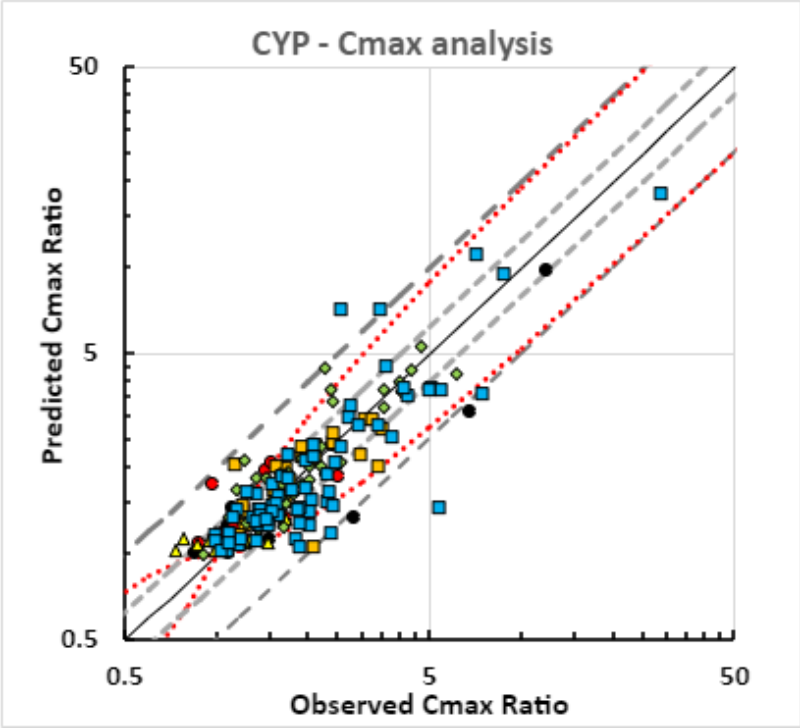
Enzyme	Competitive Inhibition	MBI	ALL
CYP1A2	42	0	42
CYP2C8	7	10	17
CYP2C9	19	3	22
CYP2C19	15	13	28
CYP2D6	34	10	44
CYP3A4/5	64	29	93
	181	65	246

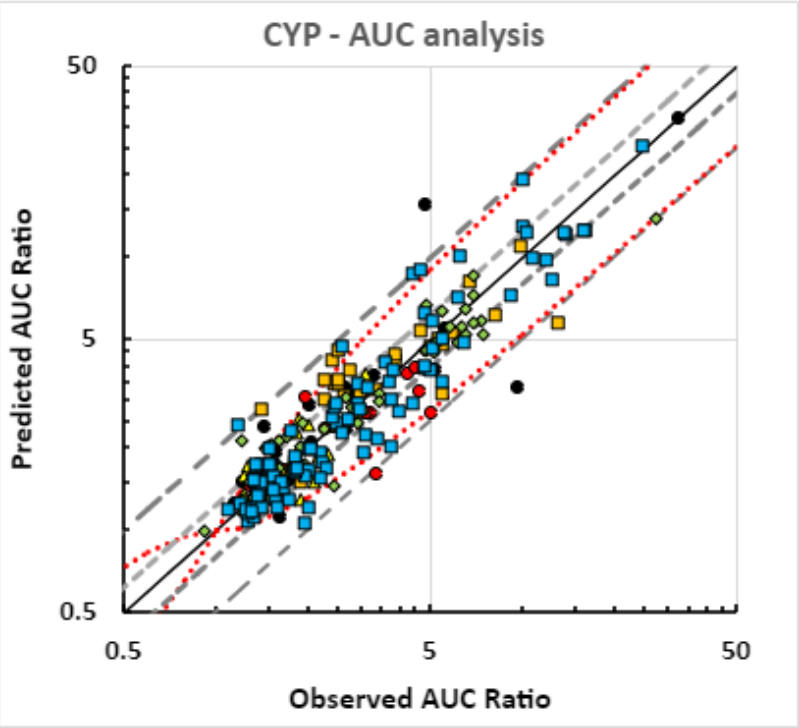


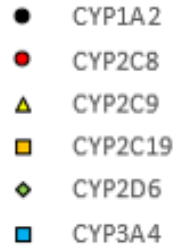
CYP3A4 DDI Matrix – Range of Substrates/Inhibitors



“Traditional” Predictive Performance of CYP-Mediated DDIs



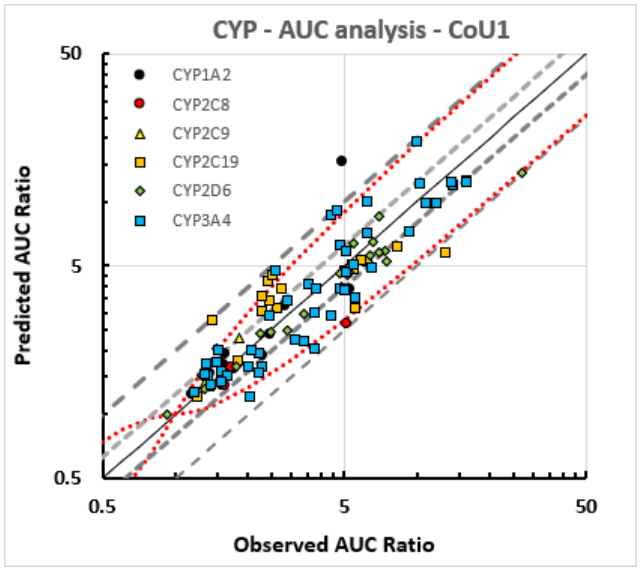


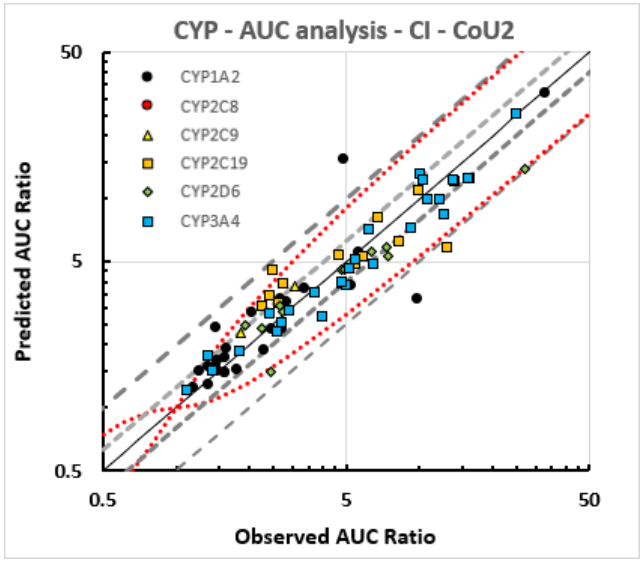


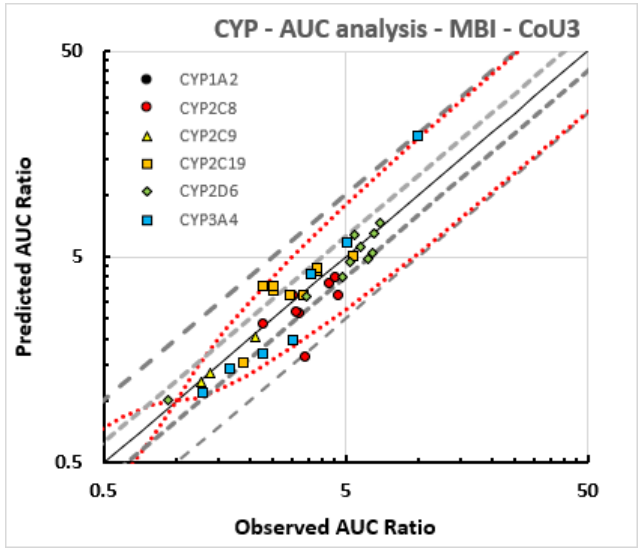
ALL - CI	V19R1 Built 96	
	Cmax Ratio	**AUC Ratio**
AFE (bias)	0.95	0.99
AAFE (precision)	1.20	1.19
Number Studies	130	187

ALL - MBI	V19R1 Built 96	
	Cmax Ratio	**AUC Ratio**
AFE (bias)	1.01	1.02
AAFE (precision)	1.23	1.25
Number Studies	60	68

Predictive Performance of CYP-Mediated DDIs – According to Each COU







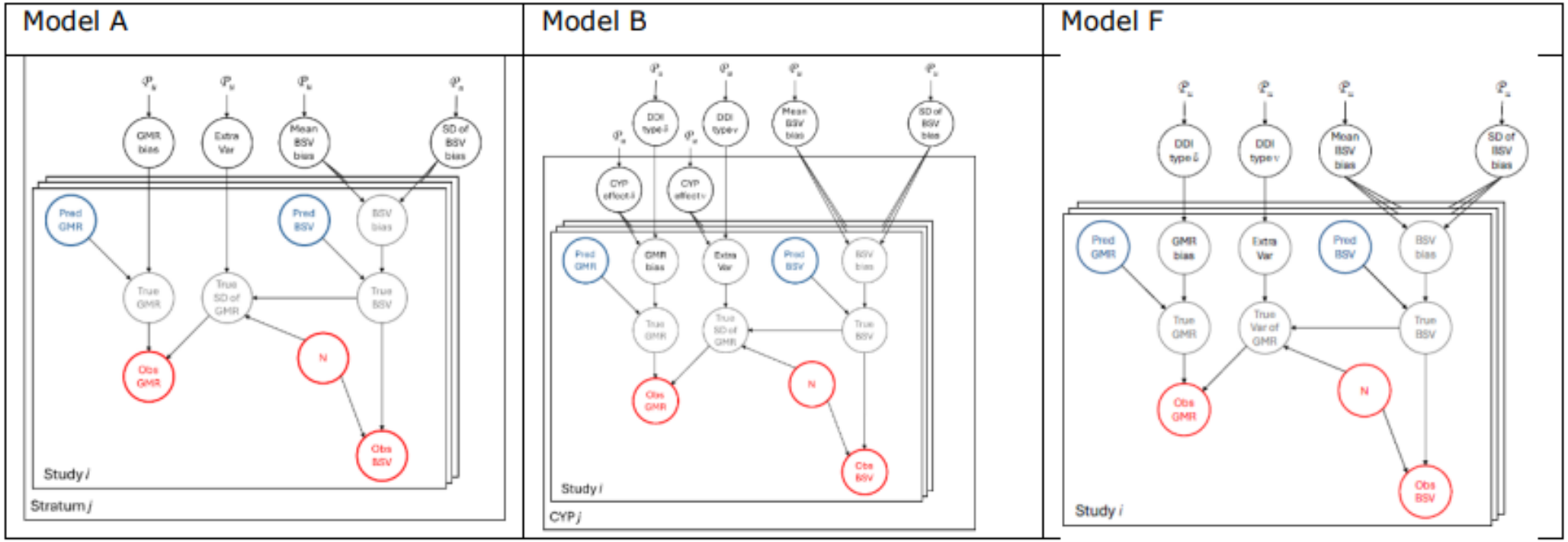
2-fold		1.5-fold		1.25-fold	
Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio
3	2	11	19	30	37
83	108	83	108	83	108
96.39	**98.15**	**86.75**	**82.41**	**63.86**	**65.74**

2-fold		1.5-fold		1.25-fold	
Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio
3	3	4	7	14	26
58	81	58	81	58	81
94.83	**96.30**	**93.10**	**91.36**	**75.86**	**67.90**

2-fold		1.5-fold		1.25-fold	
Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio
1	1	4	4	7	9
34	37	34	37	34	37
97.06	**97.30**	**88.24**	**89.19**	**79.41**	**75.68**

Bayesian Meta-Regression Models

Figure 5: Directed acyclic graph representations of model A, B and F. Observations are in red; Simcyp® predictions in blue; Latent variables in grey; estimated parameters in black



Geometric Mean Ratio – Uncertainty

Table 9: Parameter estimates for "Model F" for GMR_{AUC}

Parameter	Model F	
	Mean	SD
Mean GMR biases		
CI	-0.0568	0.0192
MBI	-0.0413	0.0404
Between-study variances		
CI	0.0321	0.0069
MBI	0.0628	0.0191
BSV* bias mean	1.4050	0.0955
BSV* bias SD	1.2889	0.0737

* BSV: Between-subject variance.

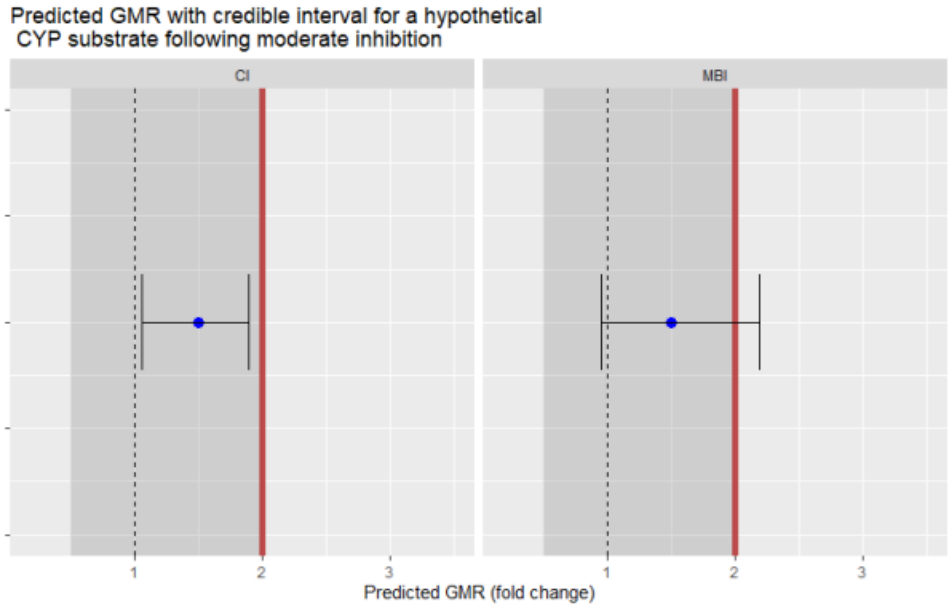
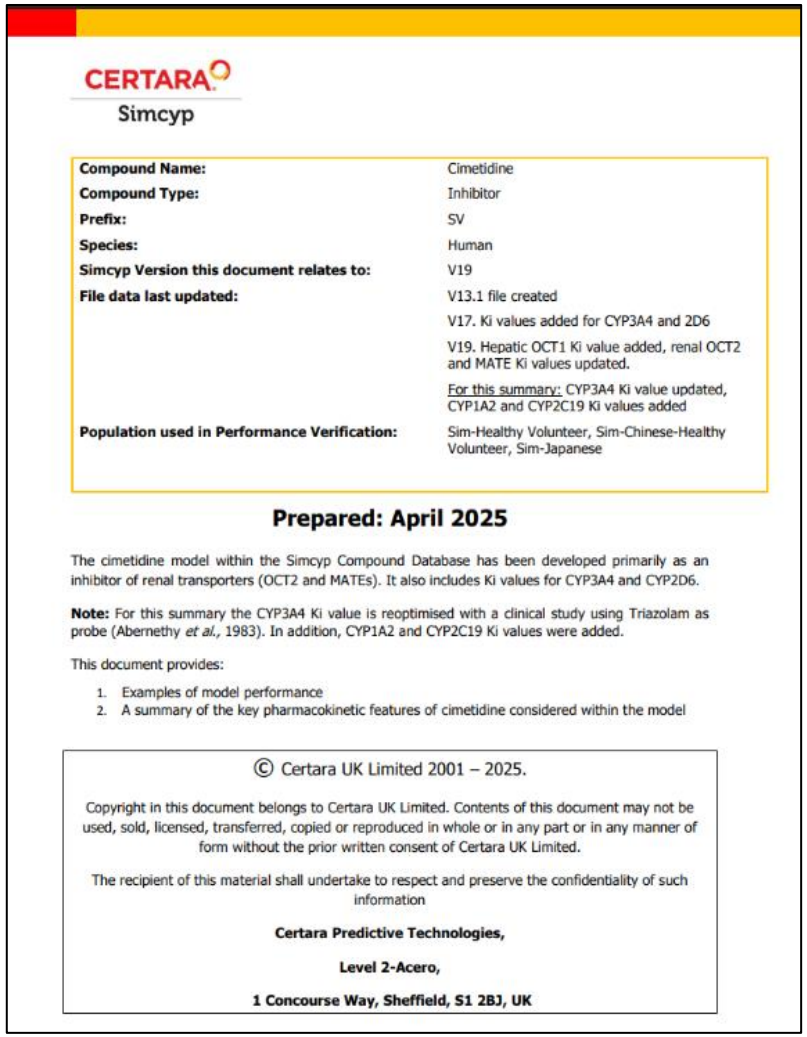


Figure 2: Predicted GMR_{AUC} following CYP inhibition for hypothetical substrate in the case of competitive inhibition (CI; left pane) or mechanism-based inhibition (MBI; right pane). The grey shaded area is defined by the no-effect boundaries of the substrate drug. The red vertical line indicates the upper boundary. The dashed vertical line indicates no inhibition. The blue dot represents the hypothetical point estimate of the GMR_{AUC} predicted by the Simcyp® platform (in this case 1.5). The error bar gives the 90% credible interval for the true GMR_{AUC}.

“Regulatory Standard” Compound File Summaries



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Compound Name:	Cimetidine
Compound Type:	Inhibitor
Prefix:	SV
Species:	Human
Simcyp Version this document relates to:	V19
File data last updated:	V13.1 file created
	V17. Ki values added for CYP3A4 and 2D6
	V19. Hepatic OCT1 Ki value added, renal OCT2 and MATE Ki values updated.
	For this summary: CYP3A4 Ki value updated, CYP1A2 and CYP2C19 Ki values added
Population used in Performance Verification:	Sim-Healthy Volunteer, Sim-Chinese-Healthy Volunteer, Sim-Japanese

Prepared: April 2025

The cimetidine model within the Simcyp Compound Database has been developed primarily as an inhibitor of renal transporters (OCT2 and MATEs). It also includes Ki values for CYP3A4 and CYP2D6.

Note: For this summary the CYP3A4 Ki value is reoptimised with a clinical study using Triazolam as probe (Abernethy *et al.*, 1983). In addition, CYP1A2 and CYP2C19 Ki values were added.

This document provides:

1. Examples of model performance
2. A summary of the key pharmacokinetic features of cimetidine considered within the model

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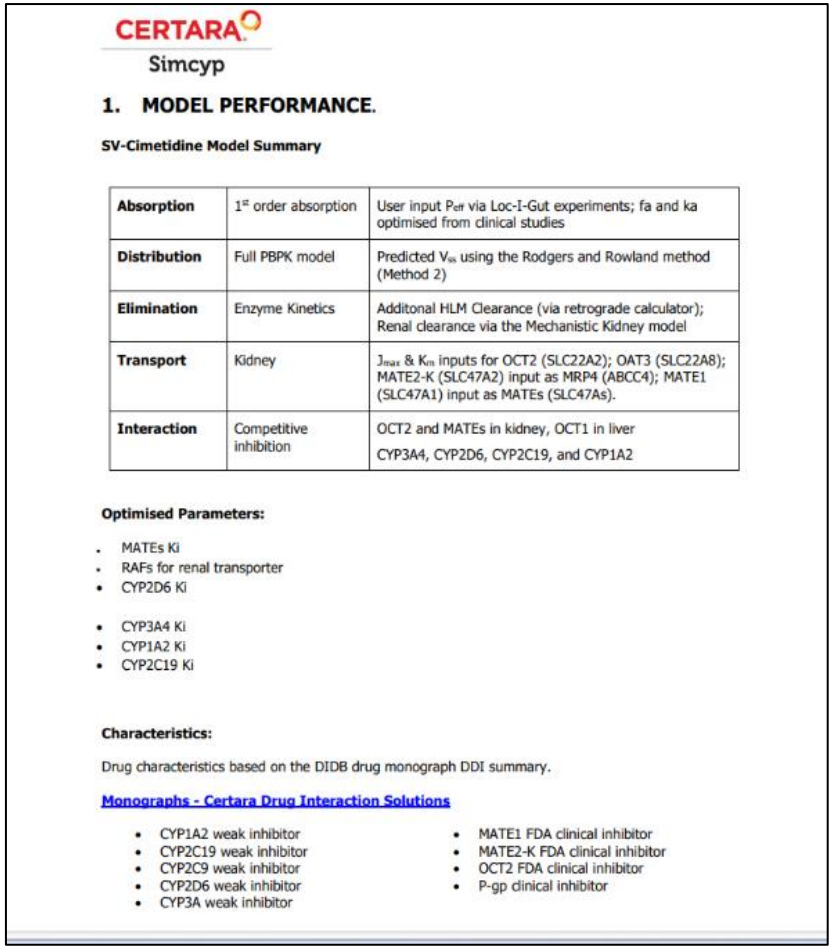

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1. MODEL PERFORMANCE.

SV-Cimetidine Model Summary

Absorption	1st order absorption	User input P_{eff} via Loc-I-Gut experiments; fa and ka optimised from clinical studies
Distribution	Full PBPK model	Predicted V_{ss} using the Rodgers and Rowland method (Method 2)
Elimination	Enzyme Kinetics	Additonal HLM Clearance (via retrograde calculator); Renal clearance via the Mechanistic Kidney model
Transport	Kidney	J_{max} & K_m inputs for OCT2 (SLC22A2); OAT3 (SLC22A8); MATE2-K (SLC47A2) input as MRP4 (ABCC4); MATE1 (SLC47A1) input as MATEs (SLC47As).
Interaction	Competitive inhibition	OCT2 and MATEs in kidney, OCT1 in liver CYP3A4, CYP2D6, CYP2C19, and CYP1A2

Optimised Parameters:

- MATEs Ki
- RAFs for renal transporter
- CYP2D6 Ki

- CYP3A4 Ki
- CYP1A2 Ki
- CYP2C19 Ki

Characteristics:

Drug characteristics based on the DIDB drug monograph DDI summary.

Monographs - Certara Drug Interaction Solutions

- CYP1A2 weak inhibitor
- CYP2C19 weak inhibitor
- CYP2C9 weak inhibitor
- CYP2D6 weak inhibitor
- CYP3A weak inhibitor
- MATE1 FDA clinical inhibitor
- MATE2-K FDA clinical inhibitor
- OCT2 FDA clinical inhibitor
- P-gp clinical inhibitor

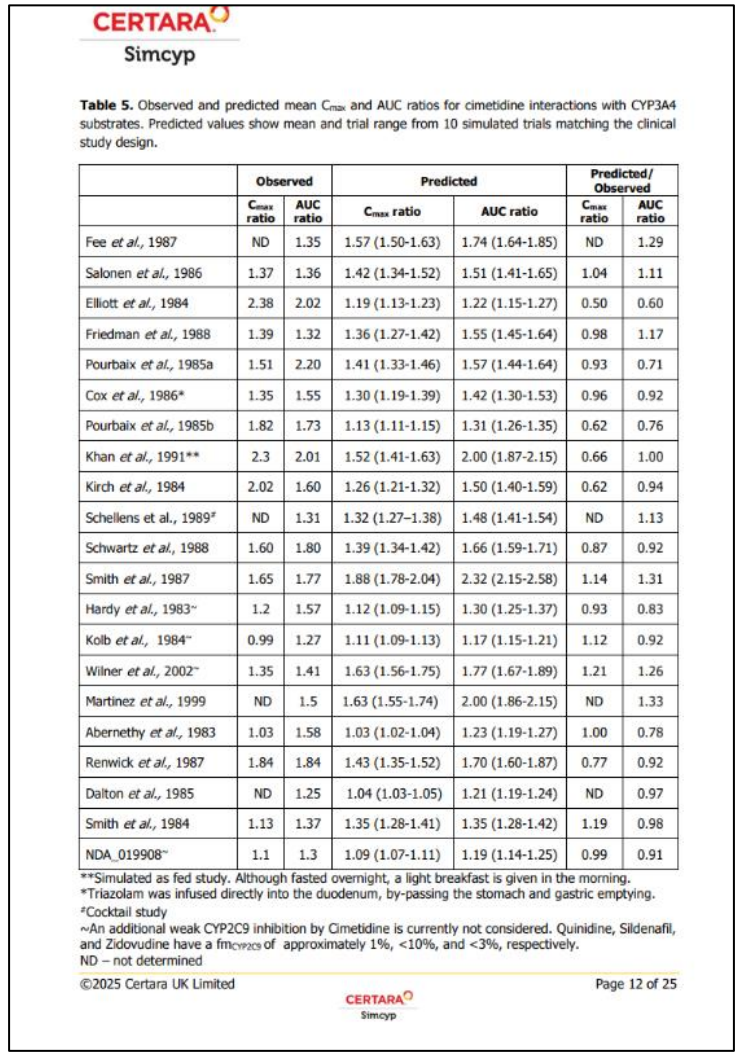

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Table 5. Observed and predicted mean C_{max} and AUC ratios for cimetidine interactions with CYP3A4 substrates. Predicted values show mean and trial range from 10 simulated trials matching the clinical study design.

	Observed		Predicted		Predicted/ Observed	
	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio
Fee *et al.*, 1987	ND	1.35	1.57 (1.50-1.63)	1.74 (1.64-1.85)	ND	1.29
Salonen *et al.*, 1986	1.37	1.36	1.42 (1.34-1.52)	1.51 (1.41-1.65)	1.04	1.11
Elliott *et al.*, 1984	2.38	2.02	1.19 (1.13-1.23)	1.22 (1.15-1.27)	0.50	0.60
Friedman *et al.*, 1988	1.39	1.32	1.36 (1.27-1.42)	1.55 (1.45-1.64)	0.98	1.17
Pourbaix *et al.*, 1985a	1.51	2.20	1.41 (1.33-1.46)	1.57 (1.44-1.64)	0.93	0.71
Cox *et al.*, 1986*	1.35	1.55	1.30 (1.19-1.39)	1.42 (1.30-1.53)	0.96	0.92
Pourbaix *et al.*, 1985b	1.82	1.73	1.13 (1.11-1.15)	1.31 (1.26-1.35)	0.62	0.76
Khan *et al.*, 1991**	2.3	2.01	1.52 (1.41-1.63)	2.00 (1.87-2.15)	0.66	1.00
Kirch *et al.*, 1984	2.02	1.60	1.26 (1.21-1.32)	1.50 (1.40-1.59)	0.62	0.94
Schellens et al., 1989#	ND	1.31	1.32 (1.27–1.38)	1.48 (1.41-1.54)	ND	1.13
Schwartz *et al.*, 1988	1.60	1.80	1.39 (1.34-1.42)	1.66 (1.59-1.71)	0.87	0.92
Smith *et al.*, 1987	1.65	1.77	1.88 (1.78-2.04)	2.32 (2.15-2.58)	1.14	1.31
Hardy *et al.*, 1983~	1.2	1.57	1.12 (1.09-1.15)	1.30 (1.25-1.37)	0.93	0.83
Kolb *et al.*, 1984~	0.99	1.27	1.11 (1.09-1.13)	1.17 (1.15-1.21)	1.12	0.92
Wilner *et al.*, 2002~	1.35	1.41	1.63 (1.56-1.75)	1.77 (1.67-1.89)	1.21	1.26
Martinez *et al.*, 1999	ND	1.5	1.63 (1.55-1.74)	2.00 (1.86-2.15)	ND	1.33
Abernethy *et al.*, 1983	1.03	1.58	1.03 (1.02-1.04)	1.23 (1.19-1.27)	1.00	0.78
Renwick *et al.*, 1987	1.84	1.84	1.43 (1.35-1.52)	1.70 (1.60-1.87)	0.77	0.92
Dalton *et al.*, 1985	ND	1.25	1.04 (1.03-1.05)	1.21 (1.19-1.24)	ND	0.97
Smith *et al.*, 1984	1.13	1.37	1.35 (1.28-1.41)	1.35 (1.28-1.42)	1.19	0.98
NDA_019908~	1.1	1.3	1.09 (1.07-1.11)	1.19 (1.14-1.25)	0.99	0.91

**Simulated as fed study. Although fasted overnight, a light breakfast is given in the morning.
*Triazolam was infused directly into the duodenum, by-passing the stomach and gastric emptying.
#Cocktail study
~An additional weak CYP2C9 inhibition by Cimetidine is currently not considered. Quinidine, Sildenafil, and Zidovudine have a fm_{CYP2C9} of approximately 1%, <10%, and <3%, respectively.
ND – not determined

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Future Qualification - Priorities

- Low hanging fruit
  - Induction
  - Induction/MBI
- COU 4 – DDI study for a perpetrator w/o a clinical DDI
- Transporter mediated DDIs
- Specific Populations
  - Pediatriacs/lactation/pregnancy
  - Organ impairment

Thank you

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