Compound Name: Midazolam

Property	Value
Compound type:	Substrate
Prefix:	Sim
Species:	Human
File data last updated:	V9: Permeability and UGT data added V15: SAC added to minimal PBPK V18: Compound type, Monoprotic base V19: ADAM absorption option added (not default) Km updated for CYP3A5 formation of 4-OH UGT data changed to HLM
Population used for verification:	Sim-Healthy Volunteer

Simcyp Version this document relates to: V19r1

Prepared: March 2025

The Sim-Midazolam model within the Simcyp Compound Database has been developed as a probe substrate of CYP3A4.

This document provides:
1. Examples of model performance
2. A summary of the key pharmacokinetic features of Sim-Midazolam considered within the model

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1. MODEL PERFORMANCE.

A. Table 1. Sim-Midazolam Model Summary

Parameter	Model	Input
Absorption	1st order absorption	User inputs for fa and Ka
Distribution	Minimal PBPK model with SAC	Fitted SAC: K_{in} K_{out} and V_{sac}. User input V_{ss} (based on clinical data)
Elimination	Enzyme kinetics	Recombinant data for CYP3A4 and CYP3A5; HLM data for UGT1A4 Renal clearance from clinical studies

OPTIMISED PARAMETERS

- k_{in}
- k_{out}
- V_{sac}

For V15 a single adjusting compartment (SAC) was added to the minimal PBPK model. The relevant parameters (k_{in}, k_{out} and V_{sac}) were fitted using the parameter estimation (PE) module in V14 to recover the PK data following an single IV dose from Kupferschmidt *et al.,* 1995.

Drug characteristics based on the DIDB drug monograph DDI summary
Monographs - Certara Drug Interaction Solutions

CYP3A FDA clinical index substrate

CYP3A sensitive substrate

Oral administration, Single dosing

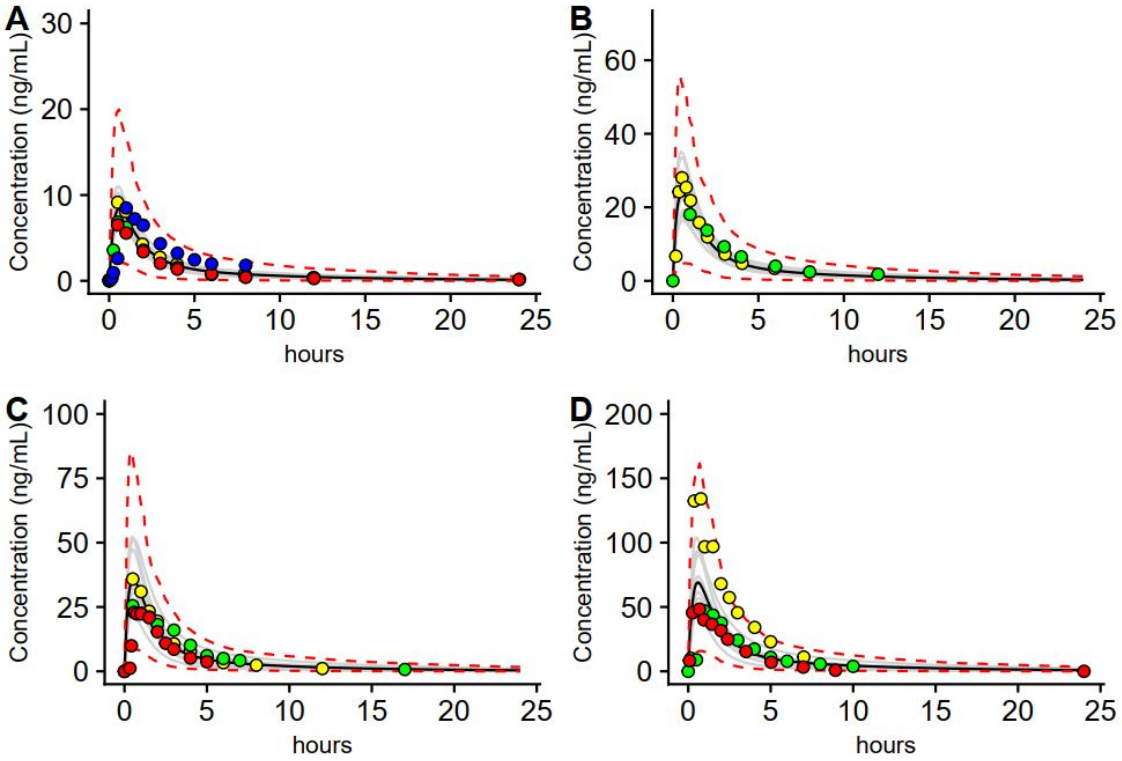

Figure 1. Simulated (black line) and observed (data points) mean plasma concentration-time profiles of midazolam after a single oral dose of (A) 2 mg (10 trials of 15 subjects, 18-55 years, 19% female) (B) 5 mg (10 trials of 12 subjects, 18-56 years, 40% female), (C) 7.5 mg (10 trials of 10 subjects, 19-44 years, 50% female) and (D) 15 mg (10 trials of 10 subjects, 19-37 years, 20% female). Observed data were extracted from (A) Krishna *et al.,* 2012 (blue), Stoch *et al.,* 2009 (red), Templeton *et al.,* 2010 (green) and Wandel *et al.,* 2000 (yellow);(B) Lee *et al.,* 2002 (red) and Ozdemir *et al.,* 2006 (green); (C) Abel *et al.,* 2008 (red), Ahonen *et al.,* 1997 (yellow), and Mandema *et al.,* 1992 (green); (D) Allonen *et al.,* 1981 (red), Backman *et al.,* 1996 (yellow), and Kupferschmidt *et al.,* 1995 (green). The grey lines represent the predictions from individual trials. The dash lines represent the 5th and 95th percentiles of the total virtual population.

Oral administration, Single dosing (log scale)

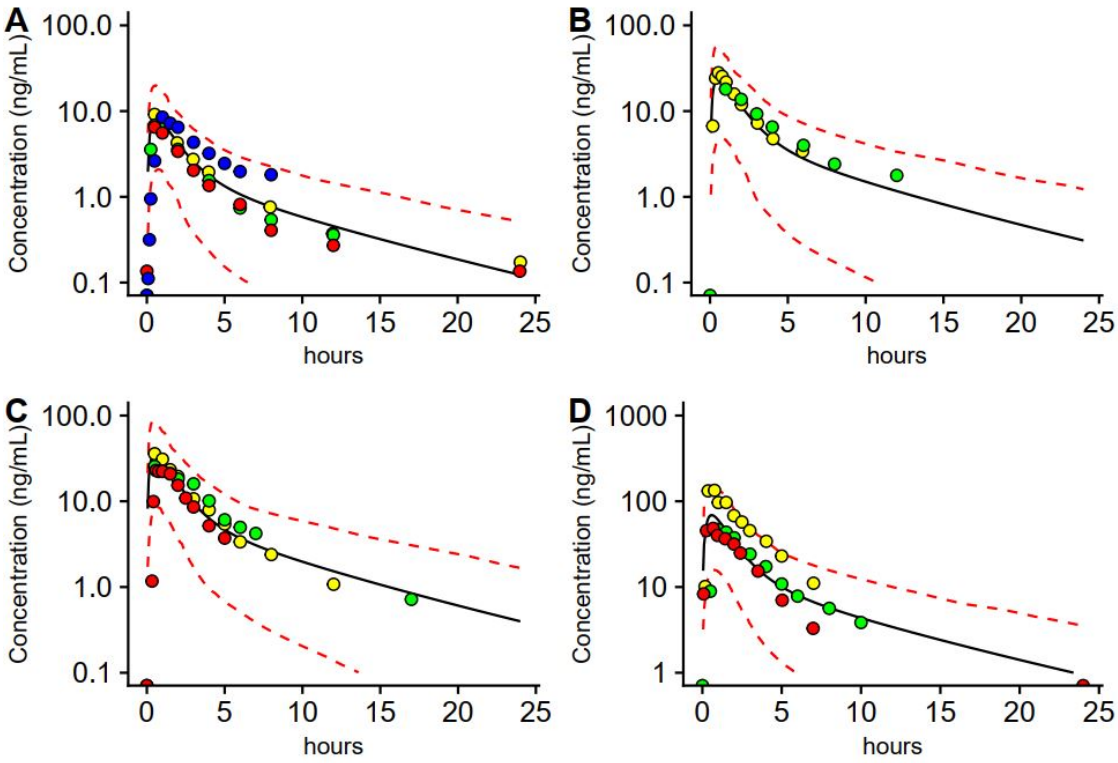

Figure 2. Simulated (black line) and observed (data points) mean plasma concentration-time profiles on a semi-logarithmic scale of midazolam after a single oral dose of (A) 2 mg (10 trials of 15 subjects, 18-55 years, 19% female), (B) 5 mg (10 trials of 12 subjects, 18-56 years, 40% female), (C) 7.5 mg (10 trials of 10 subjects, 19-44 years 50% female) and (D) 15 mg (10 trials of 10 subjects, 19-37 years, 20% female). Observed data were extracted from (A) Krishna *et al.,* 2012 (blue), Stoch *et al.,* 2009 (red), Templeton *et al.,* 2010 (green), and Wandel *et al.,* 2000 (yellow); (B) Lee *et al.,* 2002 (red) and Ozdemir *et al.,* 2006 (green); (C) Abel *et al.,* 2008 (red), Ahonen *et al.,* 1997 (yellow), and Mandema *et al.,* 1992 (green); (D) Allonen *et al.,* 1981 (red), Backman *et al.,* 1996 (yellow), and Kupferschmidt *et al.,* 1995 (green). The grey lines represent the predictions from individual trials. The dash lines represent the 5th and 95th percentiles of the total virtual population.

Intravenous administration, Single dosing

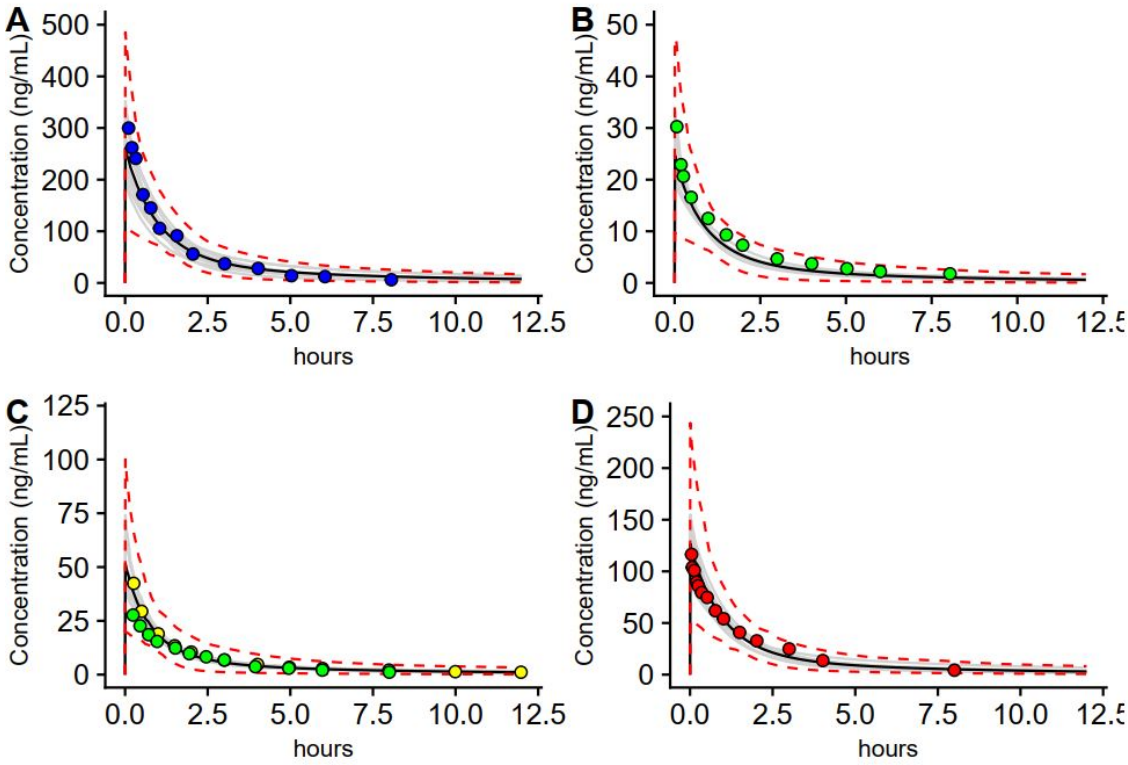

Figure 3. Simulated (black line) and observed (data points) mean plasma concentration-time profiles of midazolam after an intravenous dose of (A) 0.15 mg/kg (10 trials of 6 subjects, 22-27 years, 50% female), (B) 1 mg (10 trials of 15 male subjects, 24-44 years), (C) 2 mg (10 trials of 11 subjects, 19-43 years 16% female) and (D) 5 mg (10 trials of 8 subjects, 22-30 years, 50% female). Observed data was extracted from (A) Heizmann *et al.,* 1983 (red), (B) Wandel *et al.,* 2000 (green), (C) Farkas *et al.,* 2007 (yellow), Tsunoda *et al.,* 1999 (blue), and (D) Schwagmeier *et al.,* 1998 (orange). The grey lines represent the predictions from individual trials. The dash lines represent the 5th and 95th percentiles of the total virtual population.

Intravenous administration, Single dosing (log scale)

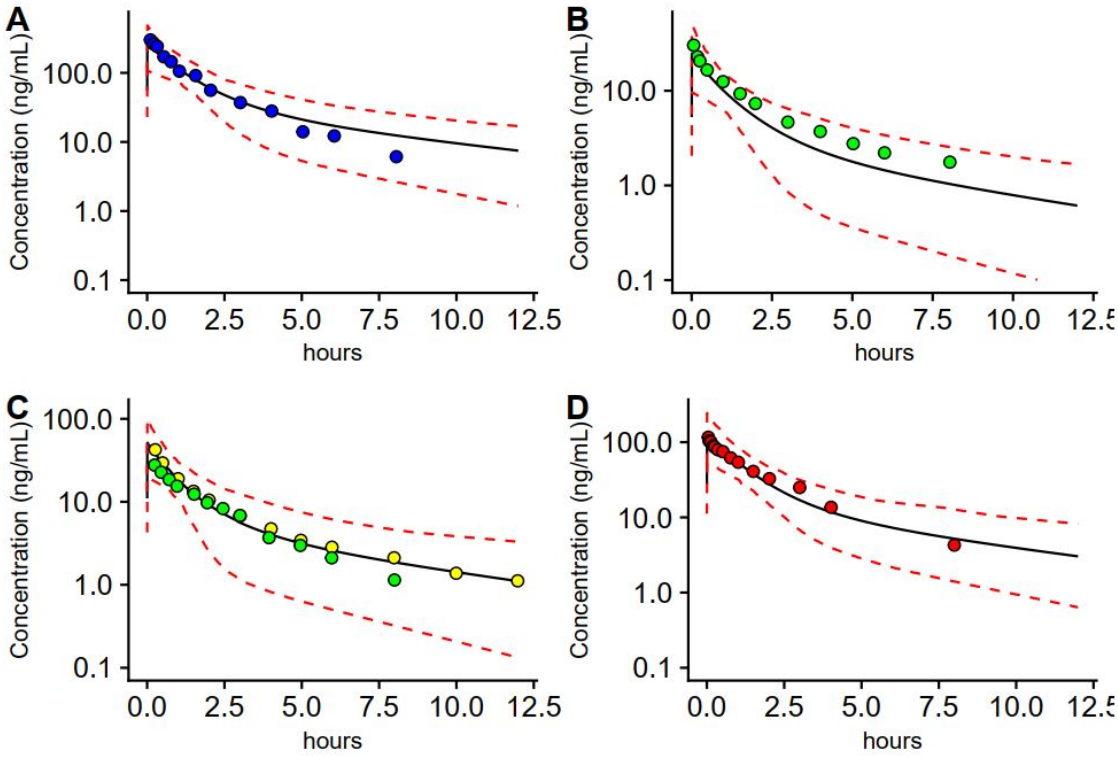

Figure 4. Simulated (black line) and observed (data points) mean plasma concentration-time profiles on a semi-logarithmic scale of midazolam after an intravenous dose of (A) 0.15 mg/kg (10 trials of 6 subjects, 22-27 years, 50% female), (B) 1 mg (10 trials of 15 male subjects, 24-44 years), (C) 2 mg (10 trials of 11 subjects, 19-43 years 16% female) and (D) 5 mg (10 trials of 8 subjects, 22-30 years, 50% female). Observed data was extracted from (A) Heizmann *et al.,* 1983 (red), (B) Wandel *et al.,* 2000 (green), (C) Farkas *et al.,* 2007 (yellow), Tsunoda *et al.,* 1999 (blue) and (D) Schwagmeier *et al.,* 1998 (orange). The grey lines represent the predictions from individual trials. The dash lines represent the 5th and 95th percentiles of the total virtual population.

2. MODEL OVERVIEW.

ABSORPTION

Oral midazolam is absorbed rapidly and almost completely from the gastrointestinal tract. Peak plasma concentrations are reached within 1 hour (Figure 5).

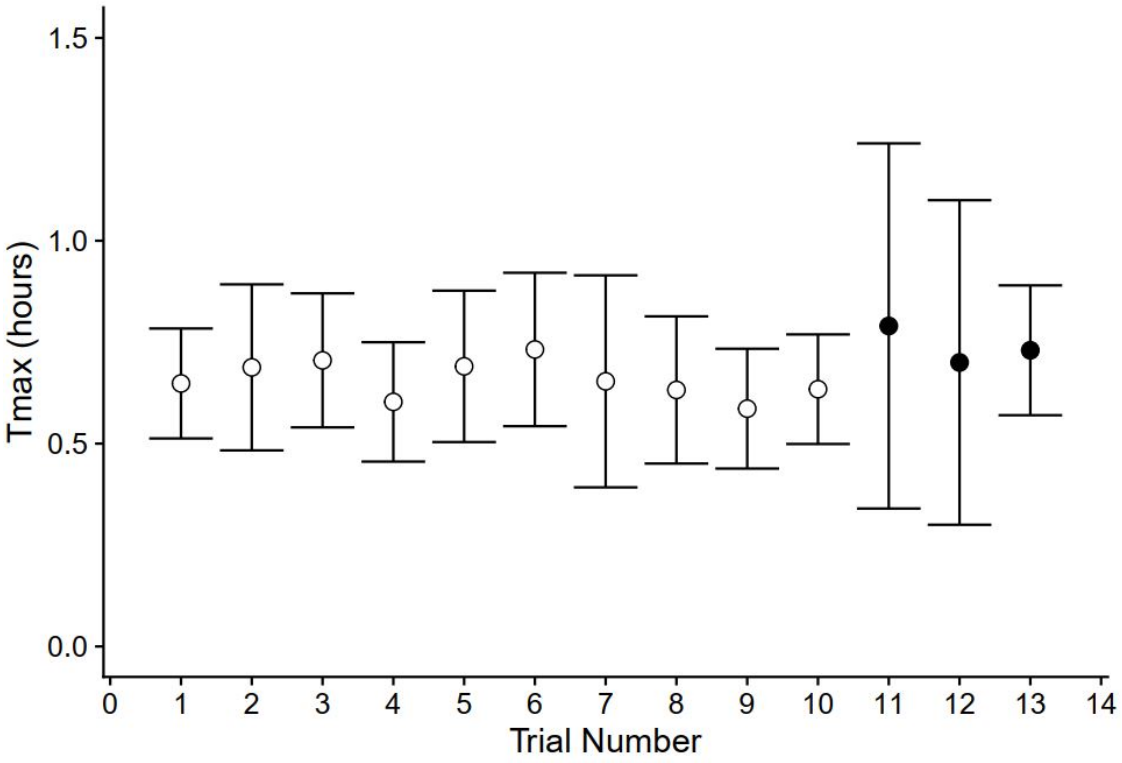

Figure 5. Simulated (open circles; mean ± SD) (10 trials of 10 subjects, 19-55 years, 50% female) and observed (closed circles; mean ± SD) values of Tmax for midazolam after a single oral dose of 7.5 mg. Predicted mean (± SD) T_{max} values (n=100) are 0.66 ± 0.16 hours. Observed data were reported by Abel *et al.,* 2008 (11), Eap *et al.,* 2004 (12), and Mandema *et al.,* 1992 (13).

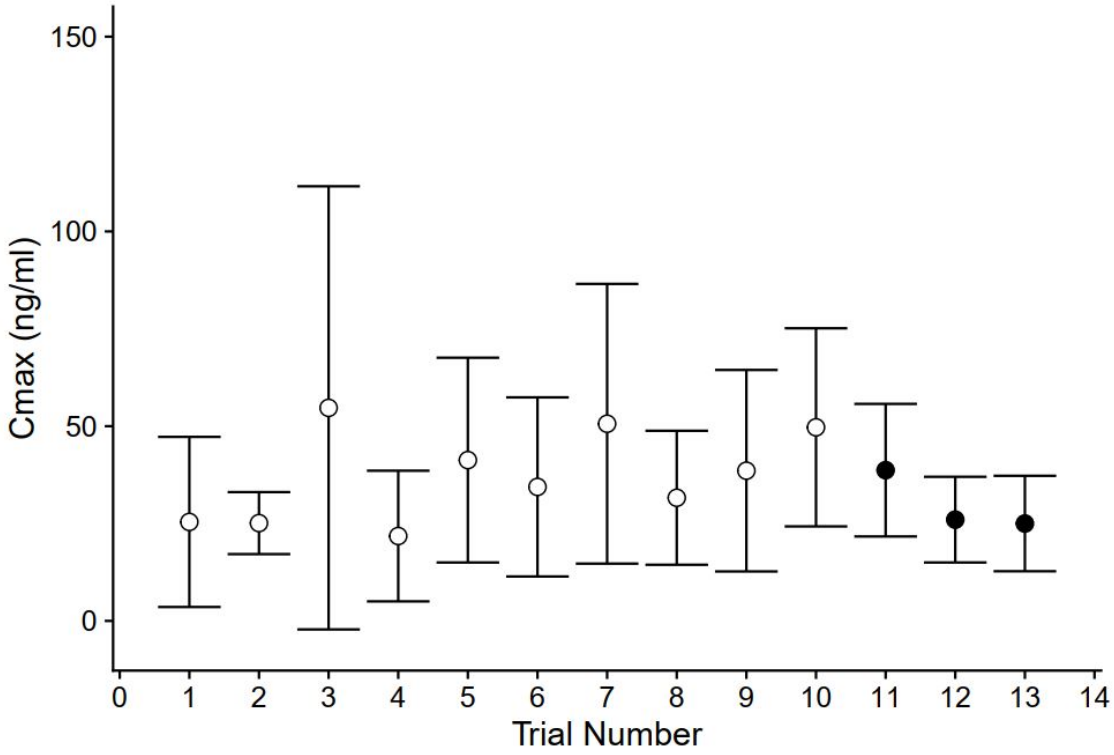

Figure 6. Simulated (open circles; mean ± SD) (10 trials of 10 subjects, 19-55 years, 50% female) and observed (closed circles; mean± SD) values of C_{max} for midazolam after a single oral dose of 7.5 mg. Predicted mean (± SD) maximal plasma concentrations (n = 100) are 37.59 ± 23.51 ng/mL. Observed data were reported by Abel *et al.,* 2008 (11), Eap *et al.,* 2004 (12), and Mandema *et al.,* 1992 (13).

DISTRIBUTION

Following intravenous administration, midazolam is rapidly and widely distributed. In the V15 update to the Sim-Midazolam file, distribution was described using a SAC compartment within the minimal PBPK model. The parameters were fitted using IV data reported by Kupferschmidt *et al.,* 1995. Values of k_{in} = 0.2 1/h, k_{out} = 0.25 1/h, V_{sac} 0.23 L/kg and V_{ss} = 0.88 L/kg are used in the Sim-Midazolam file. Midazolam is significantly bound to plasma protein (fu 0.032).

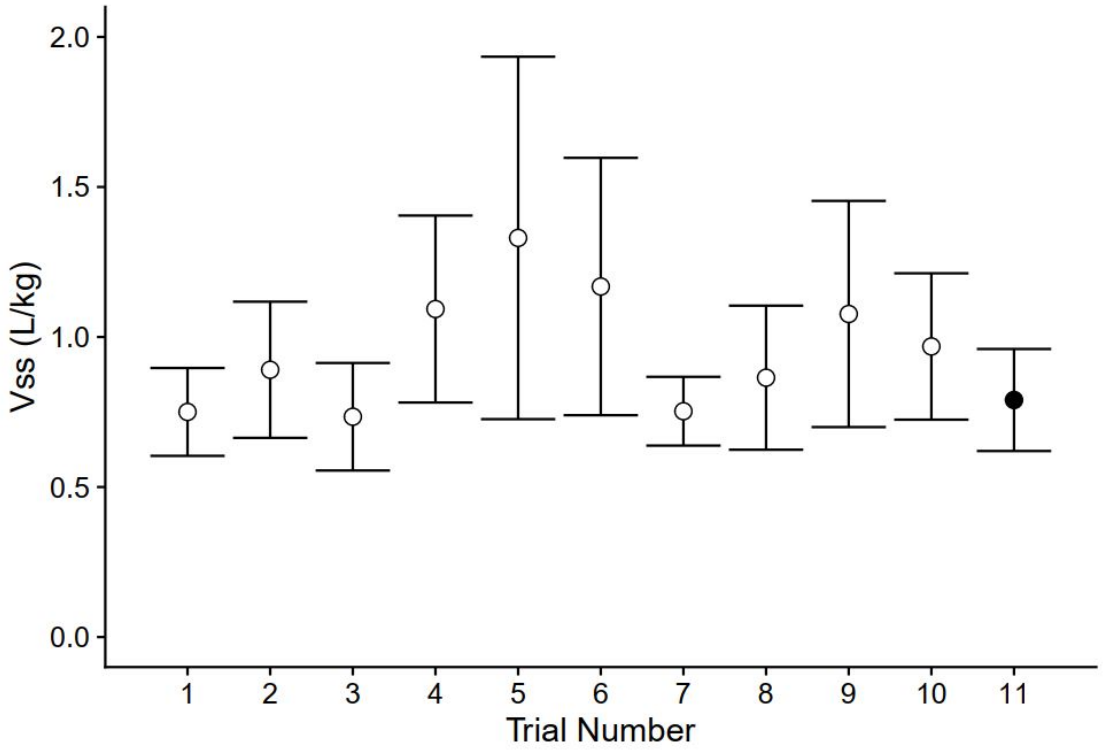

Figure 7. Simulated (open circles; mean ± SD) (10 trials of 6 male subjects, 22-27 years) and observed (closed circles; mean± SD) values of midazolam V_{ss} after an IV dose of 0.15 mg/kg. Observed data were reported by Heizmann *et al.,* 1983 (11). The mean of the virtual population (n= 60) was 0.92 ± 0.24 L/kg.

ELIMINATION

Less than 1% midazolam is excreted unchanged in the urine (Thummel *et al.,* 1996). The drug is cleared virtually entirely by CYP3A4 and CYP3A5 mediated metabolism in the gastrointestinal tract and liver (Emoto *et al.,* 2006; 2007). The primary metabolite is 1-hydroxy midazolam. Both CYP3A4 and CYP3A5 also form 4-hydroxy midazolam but to a much lesser extent. UGT1A4 has a minor (< 5%) contribution to the metabolic elimination of midazolam (Hyland *et al.,* 2009; Figure 8).

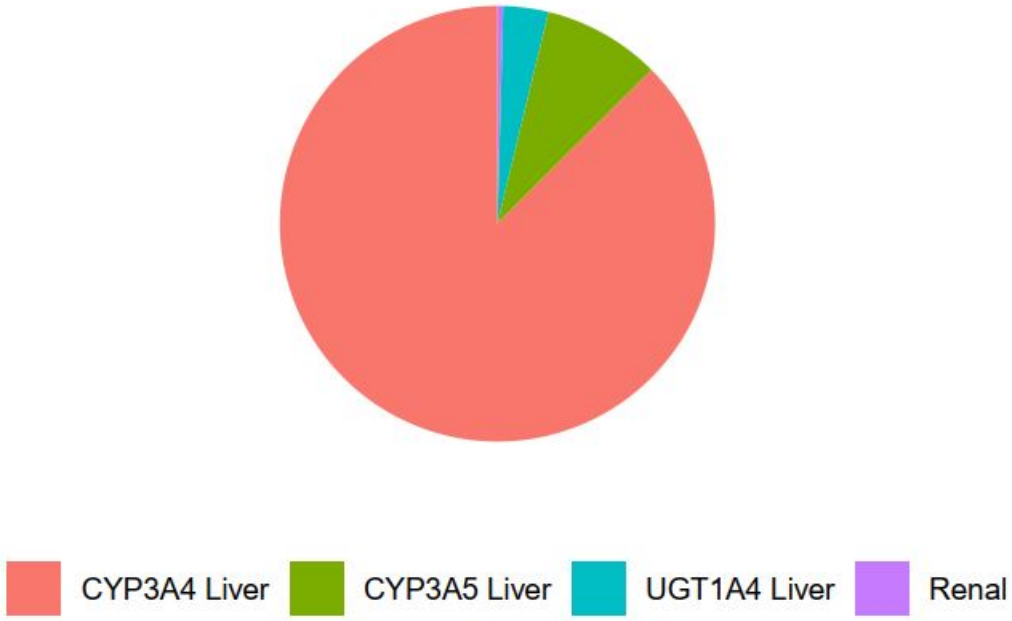

Figure 8. Predicted mean contribution of metabolic and renal clearance to the systemic elimination of midazolam (10 trials of 10 subjects, 20-50 years, 50% female).

The predicted systemic and oral clearance values are consistent with clinical data as shown in Figure 9 and Figure 10, respectively.

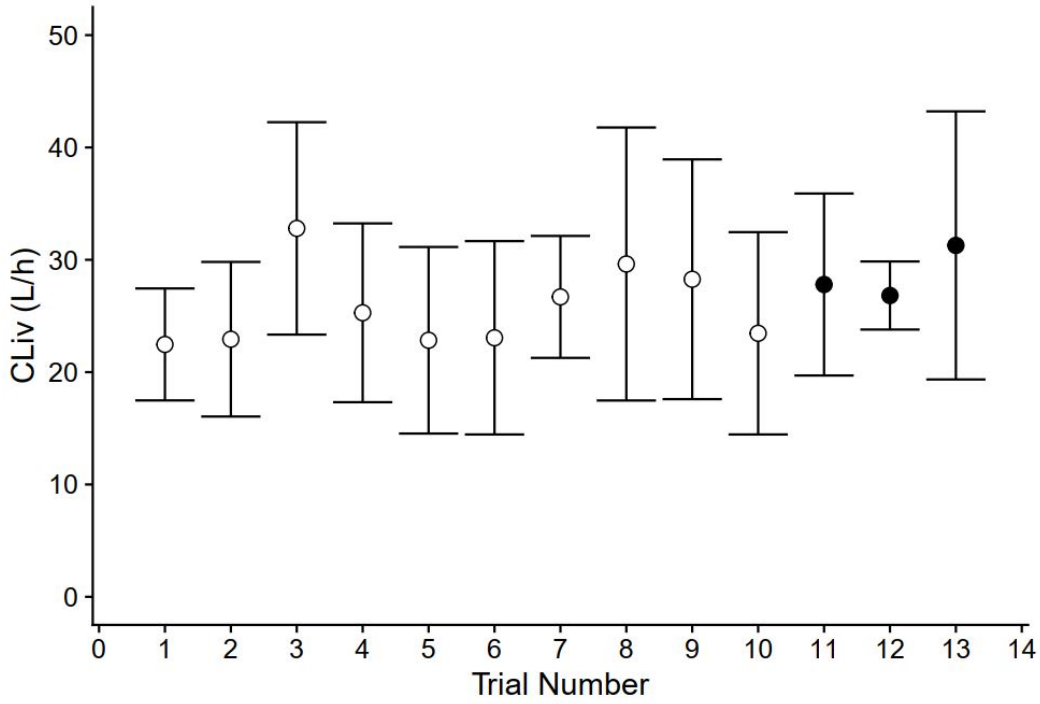

Figure 9. Simulated (open circles;mean ± SD) (10 trials of 12 subjects, 18-45 years, 35% female) and observed (closed circles; mean ± SD) values of midazolam systemic clearance after an iv dose of 2 mg. Observed data were reported by Farkas *et al.,* 2007 (11), Majumdar *et al.,* 2007 (12), and Tsunoda *et al.,* 1999 (13). The simulated population mean value was 25.13 ± 7.97 L/h.

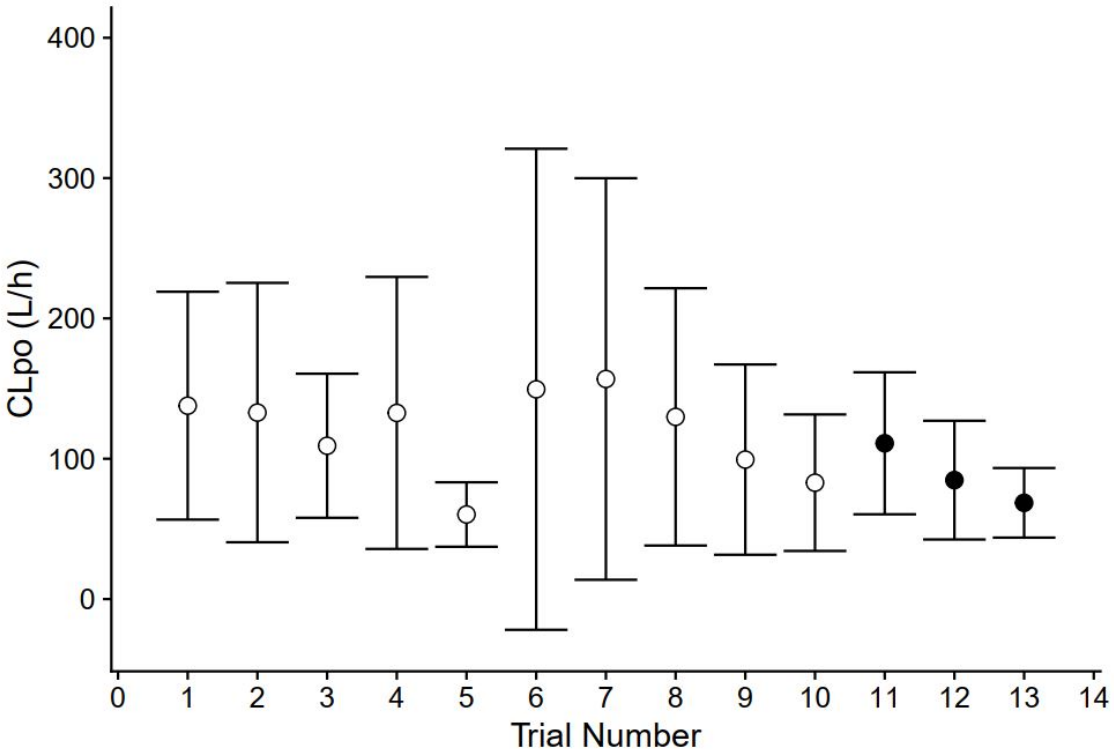

Figure 10. Simulated (open circles; mean ± SD) (10 trials of 10 subjects, 21-54 years, 22% female) and observed (closed circles; mean ± SD) values of midazolam oral clearance after an oral dose of 2 mg. Observed data were reported by Thummel *et al.,* 1996 (11) and Wandel *et al.,* 2000 (12). The simulated population mean value was 111.84 ± 99.49 L/h.

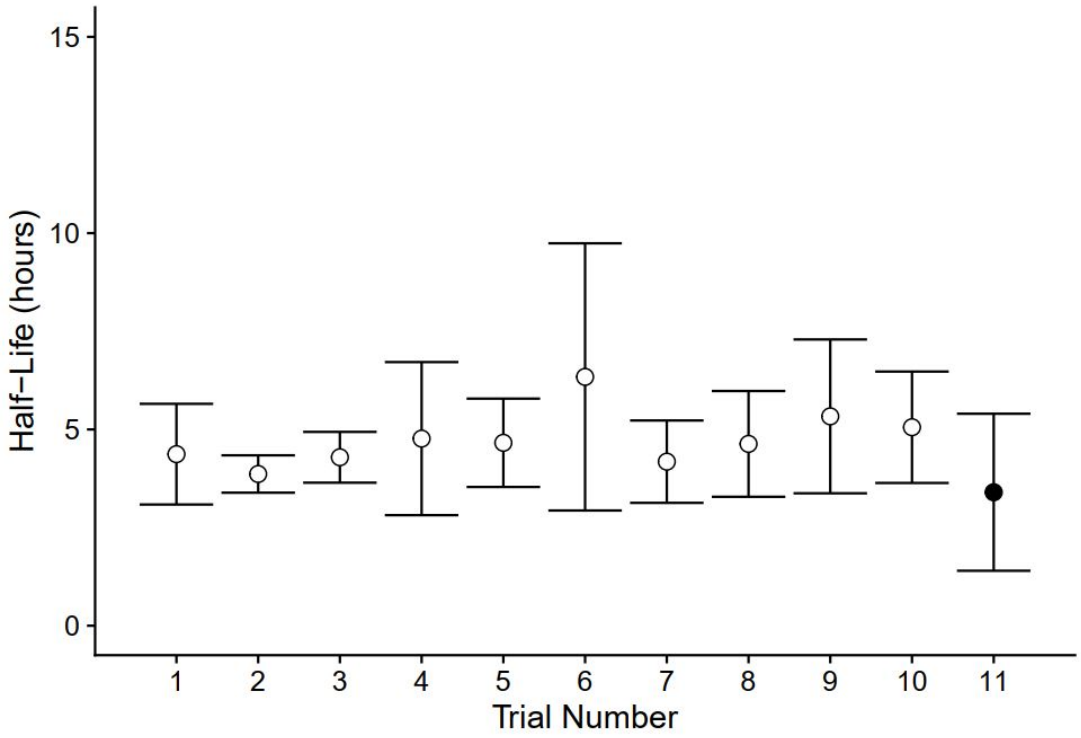

Figure 11. Simulated (open circles; mean ± SD) (10 trials of 9 subjects, 33% female 19-41 years) and observed (closed circles; mean ± SD) values of midazolam half-life after an iv dose of 2 mg. Observed data was reported by Tsunoda *et al,* 1999. (11). The simulated population mean value is 4.50 ± 0.91 h.

BIOAVAILABILITY

Simulated F, Fg and Fh are comparable to observed data. Overall bioavailability (F) 0.29 ± 0.05 Fraction escaping gut metabolism (Fg) 0.51 ± 0.1 Fraction escaping hepatic metabolism (Fh) 0.58 ± 0.09 (Taken from Galetin *et al.,* 2008)

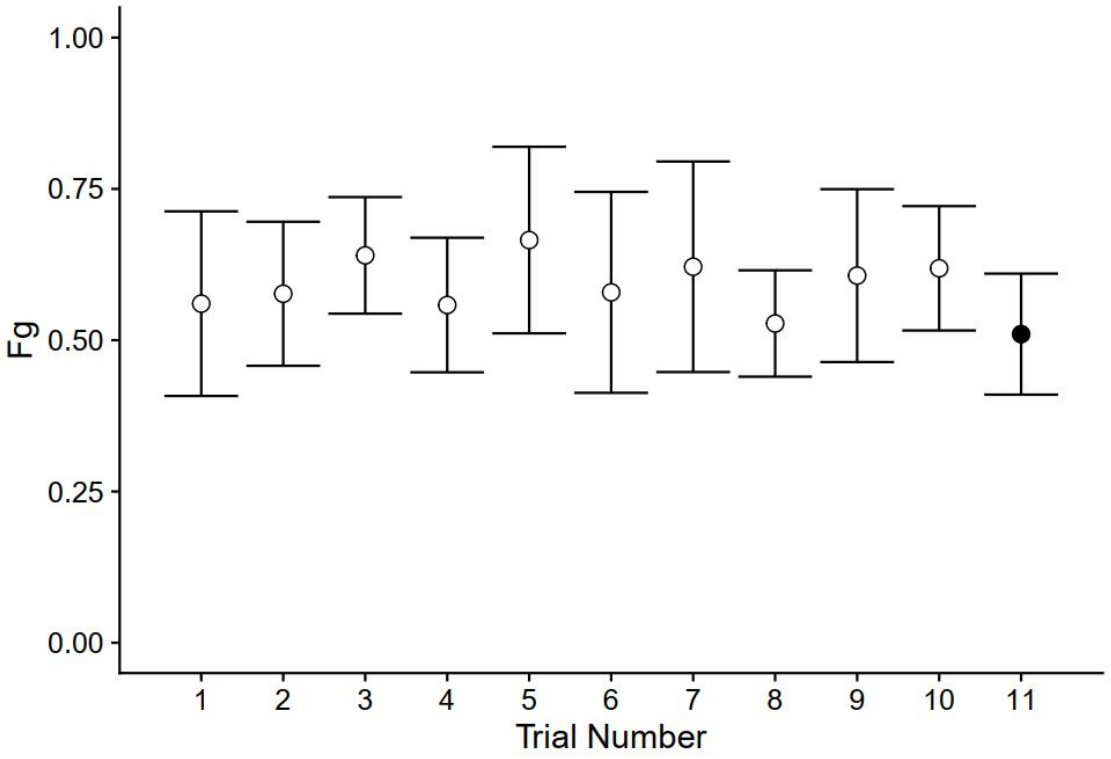

Figure 12. Simulated (open circles; mean ± SD) (10 trials of 10 subjects, 50% female 20-50 years) and observed (closed circles; mean ± SD) values of midazolam Fg values. Observed data were obtained from Galetin *et al.,* 2008 and represent the mean ± SD values reported. The simulated population mean values are 0.59.

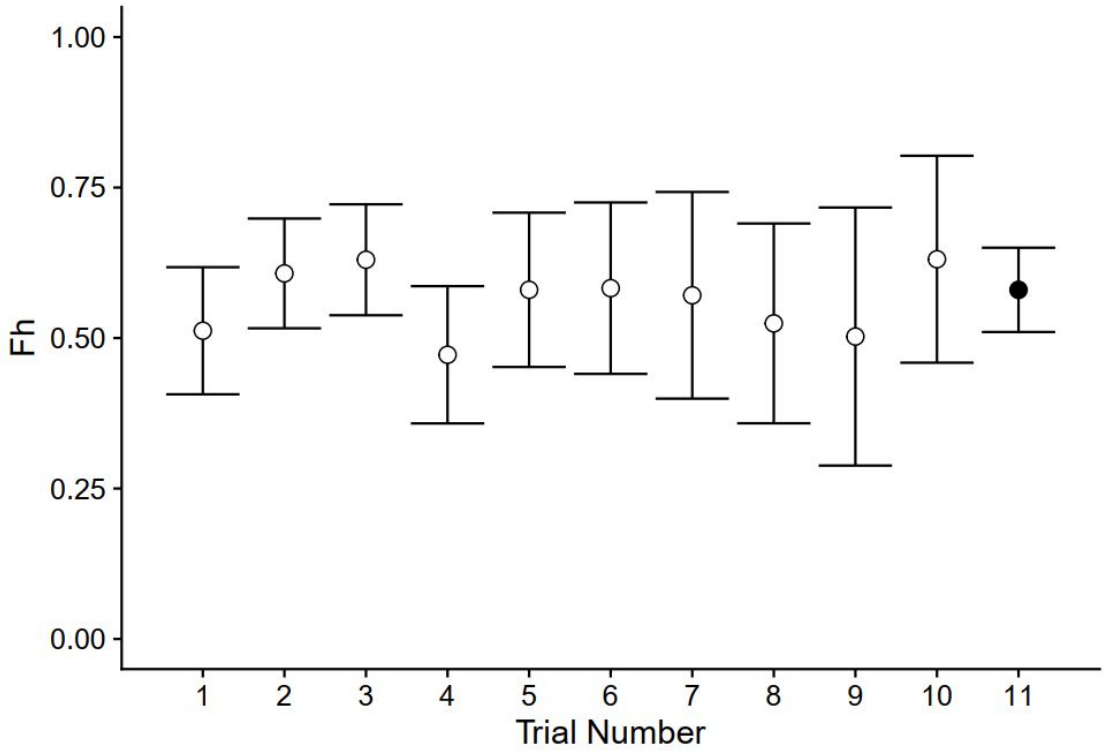

Figure 13. Simulated (open circles; mean ± SD) (10 trials of 10 subjects, 50% female 20-50 years) and observed (closed circles; mean ± SD) values of midazolam F_h values. Observed data were obtained from Galetin *et al.,* 2008 and represent the mean ± SD values reported. The simulated population mean values are 0.57.

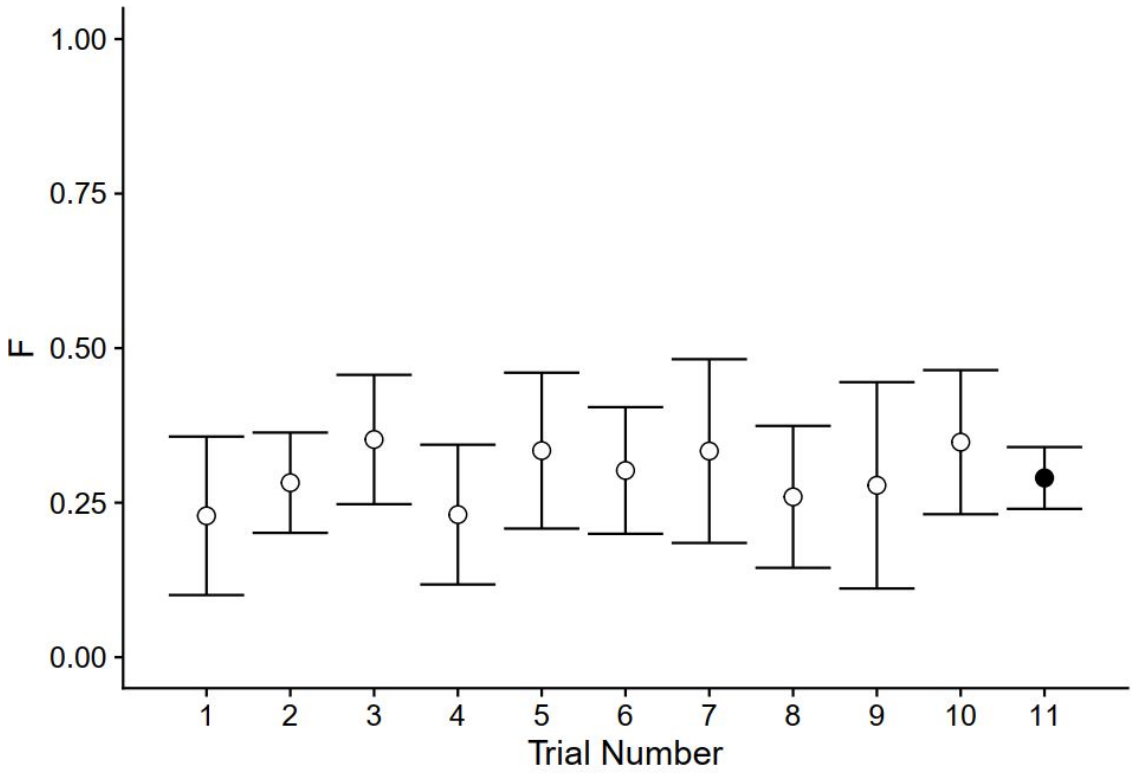

Figure 14. Simulated (open circles; mean ± SD) (10 trials of 10 subjects, 50% female 20-50 years) and observed (closed circles; mean ± SD) values of midazolam overall F values. Observed data were obtained from Galetin *et al.,* 2008 and represent the mean ± SD values reported. The simulated population mean values are 0.29.

INTERACTION

Sim-Midazolam as a victim

Investigation of Midazolam as a victim allows verification of the fm CYP3A4 used in the file. To verify the contribution of CYP3A4 within the Sim-Midazolam file, simulated drug-drug interaction (DDI) studies with the CYP3A4 inhibitors were compared to observed studies. The trial designs used were based on the clinical studies and the dosing regimen for each study is shown in Table 1. Simulated and observed AUC and C_{max} ratios are shown in Table 2.

Table 2. Dosing regimens for DDI studies

Study	Reference	Inhibitor	Midazolam
1	Ahonen *et al.*, 1997	Fluconazole 400 mg SD	7.5 mg SD (1 hr after fluconazole)
2	Olkkola *et al.*, 1994	Itraconazole 200 mg QD for 4 days	7.5 mg SD (Day 4)
3	Yeates *et al.*, 1996	Clarithromycin 250 mg BID for 5 days	15 mg SD (Day 5)
4	Backman *et al.*, 1994	Diltiazem 60 mg TID for 2 days (5 doses)	15 mg SD (Day 2) (1h after diltiazem dose 4)
5	Backman *et al.*, 1994	Verapamil 80 mg TID for 2 days (5 doses)	15 mg SD (Day 2) (1h after verapamil dose 4)
6	Tsunoda *et al.*, 1999	Ketoconazole 200 mg BID for 2 days (3 doses)	6 mg SD (12 hrs after first KTZ dose)
7	Tsunoda *et al.*, 1999	Ketoconazole 200 mg BID for 2 days (3 doses)	2 mg iv SD (12 hrs after first KTZ dose)
8	Olkkola *et al.*, 1994	Ketoconazole 400 mg QD for 4 days	7.5 mg SD (Day 4)
9	Stoch *et al.*, 2009	Ketoconazole 400 mg QD for 5 days (5 doses)	2 mg SD (Day 5)
10	Salonen *et al.*, 1986	Cimetidine 400 mg SD	15 mg SD PO, 2h after cimetidine
11	Elliott *et al.*, 1984	Cimetidine 200 mg TID with 400 mg at night on day 1. 200 mg on day 2	15 mg SD PO, day2, 2.5 h after cimetidine
12	Olkkola *et al.*, 1993	Erythromycin 500 mg TID for 6 days, day 6 2 hrs before midazolam	15 mg oral SD day 6
13	Lam *et al.*, 2003	Fluvoxamine 50 mg (36.65 mg free base) BID days 1-6, 100 mg (73.33 mg free base) BID days 7-12	10 mg SD on day 12 (1h after fluvoxamine)
14	Ahonen *et al.*, 1995	Itraconazole 100 mg QD for 4 days	7.5 mg SD on day 4
15	Backman *et al.*, 1998	Itraconazole 200 mg QD for 4 days	7.5 mg SD on day 4
16	Stoch *et al.*, 2009	Ketoconazole 400 mg oral SD	2 mg oral SD, 5 min after ketoconazole dosing

Study	Reference	Inhibitor	Midazolam
17	Eap *et al.*, 2004	Ketoconazole 200 mg BID for 2 days	75 ug SD Day 3
18	Martinez *et al.*, 1999	Cimetidine 800 mg SD	7.5 mg SD
19	Chen *et al.*, 2006	Fluvoxamine 150 mg QD oral for 28 days	0.025 mg/kg SD IV on day 28

Table 3 Observed and predicted mean C_{max} and AUC ratios for CYP3A4 inhibitors. Predicted values show mean and trial range from 10 simulated trials matching the clinical study design.

		Observed		Predicted		Predicted/Observed	
Study	Dose	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio
1	Fluconazole 400 mg SD	2.30	3.73	1.91 (1.79 to 2.16)	3.03 (2.77 to 3.39)	0.83	0.81
2	Itraconazole 200 mg QD	3.41	10.77	2.82 (2.37 to 3.57)	9.59 (8.62 to 11.76)	0.83	0.89
3	Clarithromycin 250 mg BID	2.44	3.57	2.07 (1.88 to 2.50)	4.13 (3.32 to 5.70)	0.85	1.16
4	Verapamil 80 mg TID	2.05	3.75	1.55 (1.44 to 1.65)	2.03 (1.88 to 2.27)	0.76	0.54
5	Verapamil	1.96	2.92	2.07 (1.87 to 2.23)	3.50 (3.11 to 4.04)	1.06	1.20
6	Ketoconazole 200 mg BID	4.24	15.10	3.56 (2.98 to 4.49)	12.56 (10.03 to 16.16)	0.84	0.83
7	Ketoconazole 200 mg BID	NA	4.80	1.00 (1.00 to 1.00)	4.67 (4.11 to 5.34)	NA	0.97
8	Ketoconazole 400 mg QD	4.09	15.90	3.78 (3.06 to 5.04)	12.50 (9.73 to 16.10)	0.92	0.79
9	Ketoconazole 400 mg QD*	5.42	13.96	3.76 (3.05 to 5.04)	12.12 (9.41 to 15.56)	0.69	0.87
10	Cimetidine 400 mg SD†	1.36	1.37	1.51 (1.41 to 1.65)	1.42 (1.34 to 1.52)	1.11	1.03
11	Cimetidine 200 mg MD	2.02	2.38	1.22 (1.15 to 1.27)	1.19 (1.13 to 1.23)	0.60	0.50
12	Erythromycin 500 mg MD	4.42	2.70	8.74 (6.52 to 10.6)	3.01 (2.28 to 3.78)	1.98	1.11
13	Fluvoxamine 50 mg BID	1.39	1.38	1.37 (1.29 to 1.48)	1.25 (1.21 to 1.32)	0.99	0.91
14	Itraconazole 100 mg QD	5.75	2.56	5.11 (3.77 to 6.41)	2.38 (2.15 to 2.69)	0.89	0.93
15	Itraconazole 200 mg QD†	5.17	2.91	7.15 (5.87 to 9.32)	2.82 (2.43 to 3.53)	1.38	0.97
16	Ketoconazole 400 mg SD	10.31	5.01	13.34 (11.16 to 15.87)	4.07 (3.17 to 5.05)	1.29	0.81
17	Ketoconazole 200 mg BID	6.47	3.74	4.9 (3.07 to 8.45)	2.56 (1.94 to 3.6)	0.76	0.68
18	Cimetidine 800 mg SD	1.50	NA	2 (1.86 to 2.15)	1.63 (1.55 to 1.74)	1.33	NA
19	Fluvoxamine 150 mg QD	1.49	NA	1.76 (1.63 to 1.86)	1.56 (1.48 to 1.62)	1.18	NA

Note:

AUC calulated from zero to infinity unless otherwise stated.

* Geometric mean

† AUC last

WHAT IS NOT CURRENTLY CONSIDERED IN THE MODEL:

. The ability to model the concentration time profile of the primary (active) metabolite 1-OH midazolam
. The ability to model the pharmacodynamics of midazolam and it's metabolites

Table 4 Input parameters for **SIM-Midazolam**

Parameter	Value	Method/Reference
Molecular weight (g/mol)	325.8	Pubchem
Log P	3.53	Calculated in ALOGPS 2.1
Compound Type	Monoprotic base	Simcyp data archive
pKa	6.0	Meta-analysis (Dollery, 1999; Orive *et al.*, 1989; Andersin *et al.*, 1991; Walser *et al.*, 1978;Vire *et al.*, 1986)
B/P	0.603	Meta-analysis (Allonen *et al.*, 1981; Heizmann *et al.*, 1983; Simcyp data archive)
fu	0.032	Meta-analysis (Greenblatt *et al.*, 1984; Vinik *et al.*, 1983; Thummel *et al.*, 1996)
Main binding protein	Human serum albumin	Boman, 1973
fa	1	Assumed
ka (1/h)	3	Allonen *et al.*, 1981
fu_{gut}	1	Assumed
Q_{gut} (L/h)	16.184	Predicted (Yang *et al.*, 2007)
Distribution Model	Minimal PBPk model	
V_{ss} (L/kg)	0.88	Kupferschmidt *et al.*, 1995
k_{in} (1/h)	0.2	Optimised to recover PK data following single IV dose (Kupferschmidt *et al.*, 1995)
Kout (1/h)	0.25	Optimised to recover PK data following single IV dose (Kupferschmidt *et al.*, 1995)
V_{SAC} (L/kg)	0.23	Optimised to recover PK data following single IV dose (Kupferschmidt *et al.*, 1995)
Metabolism	Enzyme kinetics	
Enzyme	CYP3A4	
Pathway	1-OH	

Parameter	Value	Method/Reference
V_{max} (pmol/min/pmol)	5.23	Meta-analysis (Carr *et al.*, 2006; Emoto *et al.*, 2003; Emoto *et al.*, 2006; Emoto *et al.*, 2007;Galetin *et al.*, 2004; Huang *et al.*, 2004; Nakajima *et al.*, 2002; Soars *et al.*, 2006; Walsky *et al.*, 2004; Weaver *et al.*, 2003; Williams *et al.*, 2002)
K_m(μM)	2.16	Meta-analysis (Carr *et al.*, 2006; Emoto *et al.*, 2003; Emoto *et al.*, 2006; Emoto *et al.*, 2007;Galetin *et al.*, 2004; Huang *et al.*, 2004; Nakajima *et al.*, 2002; Soars *et al.*, 2006; Walsky *et al.*, 2004; Weaver *et al.*, 2003; Williams *et al.*, 2002)
Enzyme	CYP3A5	
Pathway	1-OH	
V_{max} (pmol/min/pmol)	19.7	Meta-analysis (Emoto *et al.*, 2006; Emoto *et al.*, 2007;Galetin *et al.*, 2004; Huang *et al.*, 2004; Soars *et al.*, 2006; Walsky *et al.*, 2004; Williams *et al.*, 2002)
K_m(μM)	4.16	Meta-analysis (Emoto *et al.*, 2006; Emoto *et al.*, 2007; Galetin *et al.*, 2004; Huang *et al.*, 2004; Soars *et al.*, 2006; Walsky *et al.*, 2004; Williams *et al.*, 2002)
Enzyme	CYP3A4	
Pathway	4-OH	
V_{max} (pmol/min/pmol)	5.2	Meta-analysis (Emoto *et al.*, 2007; Emoto *et al.*, 2006; Galetin *et al.*, 2004; Huang *et al.*, 2004;Williams *et al.*, 2002)
K_m(μM)	31.8	Meta-analysis (Emoto *et al.*, 2007; Emoto *et al.*, 2006; Galetin *et al.*, 2004; Huang *et al.*, 2004;Williams *et al.*, 2002)
Enzyme	CYP3A5	
Pathway	4-OH	

Parameter	Value	Method/Reference
V_{max} (pmol/min/pmol)	4.03	Meta-analysis (Emoto *et al.*, 2006; Galetin *et al.*, 2004; Huang *et al.*, 2004; Williams *et al.*, 2002)
K_m(μM)	38.4	Meta-analysis (Emoto *et al.*, 2006; Galetin *et al.*, 2004; Huang *et al.*, 2004; Williams *et al.*, 2002)
Enzyme	UGT1A4	
Pathway	Pathway 1	
V_{max} (pmol/min/pmol)	445	Hyland *et al.*, 2009
K_m(μM)	40.3	Hyland *et al.*, 2009
CL_R (L/h)	0.085	Thummel *et al.*, 1996

REFERENCES:

Abel S, Russell D, Whitlock LA, Ridgway CE and Muirhead GJ (2008) Effect of maraviroc on the pharmacokinetics of midazolam, lamivudine/zidovudine, and ethinyloestradiol/levonorgestrel in healthy volunteers Br J Clin Pharmacol 65(1): 19-26.

Ahonen J, Olkkola KT and Neuvonen PJ (1997) Effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. Eur J Clin Pharmacol 51: 415-419.

Ahonen, J., Olkkola, K.T. & Neuvonen, P.J.(1995) Effect of itraconazole and terbinafine on the pharma-cokinetics and pharmacodynamics of midazolam in healthy volunteers. Br J Clin Pharmacol 40, 270-2 . Allonen H, Ziegler G and Klotz U (1981) Midazolam kinetics. Clin Pharmacol Ther 30: 653-661.

Andersin R, Tammilehto S (1991) Photochemical decomposition of midazolam IV: Study of pH-dependent stability by high-performance liquid chromatography. Journal of Pharmaceutical and Biomedical Analysis, 9(6): 451–455

Backman JT, Olkkola KT , Aranko K, Himberg JJ and Neuvonen PJ (1994) Dose of midazolam should be reduced during diltiazem and verapamil treatments. Br J Clin Pharmacol 37: 221-225.

Backman JT, Olkkola KT and Neuvonen PJ (1996) Rifampin drastically reduces plasma concentrations and effects of oral midazolam. Clin Pharmacol Ther 59: 7-13.

Backman, J.T., Kivisto, K.T., Olkkola, K.T. & Neuvonen, P.J.(1998) The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. Eur J Clin Pharmacol 54, 53-8

Carr B, Norcross R, Fang Y, Lu P, Rodrigues AD, Shou M, Rushmore T, Booth-Genthe C (2006) Characterization of the CYP3A64 enzyme: species comparisons of CYP3A substrate specificity and kinetics using baculovirus-expressed recombinant enzymes. Drug Metab Pharmacokineti 34(10): 1703-12.

Chen, Y. C., S. K. Gotzkowsky, A. N. Nafziger, R. W. Kulawy, M. L. Rocci, Jr., J. S. Bertino, Jr., and A. D. Kashuba. 2006. 'Poor correlation between 6beta-hydroxycortisol:cortisol molar ratios and midazolam clearance as measure of hepatic CYP3A activity', Br J Clin Pharmacol, 62: 187-95

Dollery, C. (Ed.) (1999) Therapeutic Drugs. Churchill Livingstone, Edinburgh.

Eap CB, Zullino D, Hustert E, Bleiber G, Golay KP, Aubert AC, Baumann P, Telenti A and Kerb R (2004) Oral administration of a low dose of midazolam (75 microg) as an in vivo probe for CYP3A activity. Eur J Clin Pharmacol 60: 237-246.

Elliott, P., J. W. Dundee, R. J. Elwood, and P. S. Collier. 1984. 'The influence of H2 receptor antagonists on the plasma concentrations of midazolam and temazepam', Eur J Anaesthesiol, 1: 245-51

Emoto C, Murase S, Sawada Y, Jones BC (2003) In vitro inhibitory effect of 1-aminobenzotriazole on drug oxidations catalyzed by human cytochrome P450 enzymes: a comparison with SKF-525A and ketoconazole. Drug Metab Pharmacokinet 18(5): 287–295.

Emoto C, Iwasaki K (2006) Enzymatic characteristics of CYP3A5 and CYP3A4: a comparison of in vitro kinetic and drug-drug interaction patterns. Xenobiotica 36(2-3): 219-33.

Emoto C, Iwasaki K (2007) Relative roles of CYP2C19 and CYP3A4/5 in midazolam 1'-hydroxylation. Xenobiotica 37(6):592-603.

Farkas D, Oleson LE, Zhao Y, Harmatz JS, Zinny MA, Court MH and Greenblatt DJ (2007) Pomegranate juice does not impair clearance of oral or intravenous midazolam, a probe for cytochrome P450-3A activity. Clin Pharmacol 47: 286-294.

Galetin A, Brown C, Hallifax D, Ito K, Houston JB (2004) Utility of recombinant enzyme kinetics in prediction of human clearance: impact of variability, CYP3A5, and CYP2C19 on CYP3A4 probe substrates. Drug Metab Dispos 32(12):1411-20.

Galetin, A., Gertz M & Houston, J.B (2008). Potential role of intestinal first-pass metabolism in the prediction of drug-drug interactions. Expert Opin Drug Metab Toxicol 4(7): 909-922.

Greenblatt DJ, Abernethy DR, Locniskar A, Harmatz JS, Limjuco RA, Shader RI (1984) Effect of age, gender, and obesity on midazolam kinetics. Anaesthesiology 61(1):27-35.

Huang W, Lin YS, McConn DJ, Calamia JC, Totah RA, Isoherranen N, Glodowski M, Thummel KE (2004) Evidence of significant contribution from CYP3A5 to hepatic drug metabolism. Drug Metab Dispos 32(12): 1434–1445.

Heizmann P, Eckert M and Ziegler WH (1983) Pharmacokinetics and Bioavailability of midazolam in man. Br J Clin Pharmacol 16: 43S-49S.

Hyland R, Osborne T, Payne A, Kempshall S, Logan YR (2009) In vitro and in vivo glucuronidation of midazolam in humans. Br J Clin Pharmacol 67: 445-454.

Krishna G, Ma L, Prasad P, Moton A, Martinho M and O'Mara E (2012) Effect of posaconazole on the pharmacokinetics of simvastatin and midazolam in healthy volunteers. Expert Opin Drug Metab Toxicol 8 (1): 1-10.

Kupferschmidt HH, Ha HR, Ziegler WH, Meier PJ and Krahenbuhl S (1995) Interaction between grapefruit juice and midazolam in humans. Clin Pharmacol Ther 58: 20-28.

Lam, Y. W., C. L. Alfaro, L. Ereshefsky, and M. Miller. 2003. 'Pharmacokinetic and pharmacodynamic interactions of oral midazolam with ketoconazole, fluoxetine, fluvoxamine, and nefazodone', J Clin Pharma-col, 43: 1274-82.

Lee JL, Chaves-Gnecco D, Kroboth PD, Wilson JW and Frye RF (2002) Application of semisimultaneous midazolam administration for hepatic and intestinal cytochrome P450 3A phenotyping. Clin Pharmacol Ther 72: 718-728.

Majumdar AK, Yan KX, Selverian DV, Barlas S, Constanzer M, Dru J, McCrea JB, Ahmed T, Frick GS, Kraft WK, Petty KJ and Greenberg HE (2007) Effect of Aprepitant on the pharmacokinetics of Intravenous Midazolam. J Clin Pharmacol 47: 744-750.

Mandema JW, Tuk B, van Steveninck AL, Breimer DD, Cohen AF and Danhof M (1992) Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteers. Clin Pharmacol Ther 51: 715-728.

Martinez, C., C. Albet, J. A. Agundez, E. Herrero, J. A. Carrillo, M. Marquez, J. Benitez, and J. A. Ortiz. 1999. 'Comparative in vitro and in vivo inhibition of cytochrome P450 CYP1A2, CYP2D6, and CYP3A by H2-receptor antagonists', Clin Pharmacol Ther, 65: 369-76.

Nakajima M, Tane K, Nakamura S, Shimada N, Yamazaki H, Yokoi T (2002) Evaluation of approach to predict the contribution of multiple cytochrome P450s in drug metabolism using relative activity factor. J Pharm Sci 91(4): 952–963.

Olkkola, K. T., K. Aranko, H. Luurila, A. Hiller, L. Saarnivaara, J. J. Himberg, and P. J. Neuvonen. 1993. 'A potentially hazardous interaction between erythromycin and midazolam', Clin Pharmacol Ther, 53: 298-305

Olkkola KT, Backman JT and Neuvonen PJ (1994) Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. Clin Pharmacol Ther 55: 481-485.

Orive MM, Alonso RM, Jiménez RM (1989) Voltammetric determination of benzodiazepines in pharmaceu-tical preparations. Microchimica Acta, 97(3-4): 181–190.

Ozdemir M, Crewe KH, Tucker GT and Rostami-Hodjegan A (2006) The impact of dose staggering on the inhibitory effect of ketoconazole on midazolam clearance and its prediction using physiologically based pharmacokinetic modelling and simulations. Drug Met Reviews 38 suppl 1: P103.

Salonen, M., E. Aantaa, L. Aaltonen, and J. Kanto. 1986. 'Importance of the interaction of midazolam and cimetidine', Acta Pharmacol Toxicol (Copenh), 58: 91-5.

Schwagmeier R, Alincic S and Striebel HW (1998) Midazolam pharmacokinetics following intravenous and buccal administration. Br J Clin Pharmacol 46: 203-206.

Soars MG, Grime K, Riley RJ (2006) Comparative analysis of substrate and inhibitor interactions with CYP3A4 and CYP3A5. Drug Metab Dispos 36(4): 287-99.

Stoch SA, Friedman E, Maes A, Yee K, Xu Y, Larson P, Fitzgerald M, Chodakewitz J and Wagner JA (2009) Effect of different durations of ketoconazole dosing on the single-dose pharmacokinetics of Midazolam: Shortening the paradigm. J Clin Pharmacol 49: 398-406.

Templeton I, Peng C-C, Thummel KE, Davis C, Kunze KL and Isoherranen N (2010) Accurate prediction of dose-dependent CYP3A4 Inhibition by Itraconazole and Its metabolites from In Vitro inhibition data. Clin Pharmacol Ther 88 (4): 499-505.

Thummel KE, O'Shea D, Paine MF, Shen DD, Kunze KL, Perkins JD and Wilkinson GR (1996) Oral first-pass elimination of midazolam involves both gastrointestinal and hepatic CYP3A-mediated metabolism. Clin Pharmacol Ther 59: 491-502.

Tsunoda SM, Velez RL, von Moltke LL and Greenblatt DJ (1999) Differentiation of intestinal and hepatic cytochrome P450 3A activity with use of midazolam as an in vivo probe: effect of ketoconazole. Clin Pharmacol Ther 66: 461-471.

Vire JC, Gallo Hermosa B, Patriarche GJ (1986) Electrochemical study and hydrolysis kinetic of imidazo-and triazolobenzodiazepines. Analytical Letters, 19(15-16): 1839–1851.

Vinik HR, Reves JG, Greenblatt DJ (1983) The pharmacokinetics of midazolam in chronic renal failure patients. Anesthesiology 59(5): 390-4.

Walser A, Benjamin LE, Flynn T, Mason C, Schwartz R, Fryer RI (1978) Quinazolines and 1,4-benzodiazepines. 84. Synthesis and reactions of imidazo benzodiazepines. Journal of Organic Chemistry, 43(5): 936–944.

Wandel C, Witte JS, Hall JM, Stein CM, Wood AJJ, and Wilkinson GR (2000) CYP3A activity in American men: Population differences a nd f unctional e ffect of th e CY P3A4*1B 5 -promoterе gion polymorphism. Clin Pharmacol Ther 68 (1): 82-91.

Walsky RL, Obach RS (2004) Validated assays for human cytochrome P450 activities. Drug Metab Dispos 32(6): 647–660.

Weaver R, Graham KS, Beattie IG, Riley RJ (2003) Cytochrome P450 inhibition using recombinant proteins and mass spectrometry/multiple reaction monitoring technology in a cassette incubation. Drug Metab Dispos 31(8): 955–966.

Williams JA, Ring BJ, Cantrell VE, Jones DR, Eckstein J, Ruterbories K, Hamman MA, Hall SD, Wrighton SA (2002) Comparative metabolic capabilities of CYP3A4, CYP3A5, and CYP3A7. Drug Metab Dispos 30(8): 883–891.

Yang, J., M. Jamei, K. R. Yeo, G. T. Tucker, and A. Rostami-Hodjegan (2007). "Prediction of intestinal first-pass drug metabolism". In: Curr Drug Metab 8.7, pp. 676–84.

Yeates RA, Laufen H and Zimmerman T (1996) Interaction between midazolam and clarithromycin: comparison with azithromycin. Int J Clin Pharmacol and Therap 34 (9): 400-405.