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Quantification of the time course of CYP3A inhibition, activation, and induction using a population pharmacokinetic model of microdosed midazolam continuous infusion

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Table S1 Individual midazolam pharmacokinetic parameters after 3 µg bolus dose (bolus period)

ID	Pharmacokinetic parameter [unit]						
	C_{max} [pg/mL]	T_{max} [h]	$AUC_{0-\infty}$ [pg·h/mL]	$T_{1/2}$ [h]	Clearance [mL/min]	V [L]	V_{ss} [L]
1	130	0.0333	110	2.36	456	93.2	66.3
2	132	0.0333	98.3	2.48	509	109	77.1
3	134	0.0333	103	1.68	485	70.3	61.8
4	72.9	0.0333	83.5	2.01	599	104	69.4
5	74.3	0.0333	68.3	1.71	732	109	86.0
6	136	0.0333	86.8	2.31	576	115	83.3
7	307	0.0833	123	1.71	405	60.0	49.4
8	88.4	0.0333	141	1.98	354	60.5	50.8
9	112	0.0333	91.1	2.43	549	115	73.3
10	417	0.0333	147	2.55	340	75.1	49.0
11	131	0.0333	127	2.11	393	71.8	53.6
12	247	0.0333	116	1.83	429	68.0	50.2
13	126	0.0333	148	1.64	337	47.8	40.9
14	79.4	0.0333	68.6	1.88	729	118	81.1
15	219	0.0333	114	1.82	440	69.3	43.6
16	80.1	0.0333	92.1	1.75	543	82.0	64.5
17	101	0.0333	97.2	2.51	514	112	88.9
18	91.1	0.0333	125	1.87	399	64.5	62.8
19	106	0.0333	109	2.22	457	87.7	66.5
20	153	0.0333	122	2.28	411	81.2	55.2
21	129	0.0333	128	2.18	391	73.9	51.1
22	135	0.0333	133	2.35	375	76.5	65.8
23	122	0.0333	105	1.73	476	71.3	64.6
24	85.0	0.0333	102	2.73	492	116	91.8
Mean			110	2.09	475	85.5	64.5
Standard deviation			21.8	0.32	104.8	21.1	14.4
%CV			19.8	15.4	22.1	24.7	22.3

Noncompartmental analysis calculated by Kinetica 5.0

$AUC_{0-\infty}$ Area under the curve from time zero to infinity; *C_{max}* Maximum concentration; *CV* Coefficient of variability; *T_{max}* Time of maximum concentration; *V* volume of distribution; *V_{ss}* Volume of distribution at steady state

Table S2 Calculated midazolam dosing for period two (perpetrator period)

ID	Calculated midazolam dose for perpetrator period	
	Bolus dose [µg]	Infusion rate [µg/h]
1	4.40	2.80
2	5.10	3.10
3	4.10	2.90
4	4.60	3.60
5	5.70	4.40
6	5.60	3.50
7	3.30	2.40
8	3.40	2.10
9	4.90	3.30
10	3.40	2.10
11	3.60	2.40
12	3.30	2.60
13	2.70	2.00
14	5.40	4.40
15	2.90	2.70
16	4.30	3.30
17	5.90	3.10
18	4.20	2.40
19	4.40	2.70
20	3.70	2.50
21	3.40	2.30
22	4.40	2.30
23	4.30	2.90
24	6.10	3.00
Mean	4.30	2.87
Standard deviation	0.97	0.65
%CV	22.6	22.6

CV Coefficient of variability

Table S3 Individuals' demographics (n=24; 12 males, 12 females)

Variable	Mean	Median	SD	CV%	Range
Age [years]	29.6	27.0	7.55	25.5	22.0–54.0
Height [m]	1.73	1.73	0.0846	4.90	1.59–1.90
Weight [kg]	71.3	69.3	11.09	15.6	55.3–90.5
BMI [kg/m^2]	23.9	23.7	2.70	11.3	19.6–29.9

BMI Body mass index, *CV* coefficient of variation, *SD* standard deviation

Table S4 Results of covariate analysis: Estimated midazolam clearance per time interval and perpetrator type

Study arm	Time interval (time relative to perpetrator administration [h])	Clearance [L/h]	Absolute change in clearance compared to placebo arm [L/h]	Relative change in clearance compared to placebo arm (%)
Placebo[a]		43.9	n.a.	n.a.
Oral voriconazole	[0, 1]	26.4	-17.5	-39.9
	(1, 2]	31.2	-12.7	-29.0
	(2, 3]	33.5	-10.4	-23.8
	(3, 4]	29.9	-14.0	-31.9
	(4, 5]	15.8	-28.1	-63.9
	(5, 6]	20.2	-23.7	-54.0
	(6, 7]	12.9	-30.9	-70.6
	(7, 8]	13.4	-30.4	-69.4
Intravenous voriconazole	[0, 1]	36.6	-7.26	-16.6
	(1, 3]	39.0	-4.88	-11.1
	(3, 4]	37.2	-6.67	-15.2
	(4, 5]	27.9	-15.9	-36.4
	(5, 6]	26.7	-17.2	-39.3
	(6, 7]	17.1	-26.8	-61.1
	(7, 8]	18.3	-25.6	-58.3
Oral efavirenz	[0, 2]	50.5	6.60	15.0
	(2, 3]	69.8	25.9	59.1
	(3, 4]	68.5	24.6	56.0
	(4, 5]	56.4	12.5	28.5
	(5, 6]	58.5	14.6	33.3
Oral rifampicin	[22, 24]	56.1	12.3	27.9
	(24, 26]	51.6	7.74	17.6
	(26, 28]	54.3	10.4	23.7
	(28, 30]	64.4	20.5	46.7
	(30, 34]	48.4	4.49	10.2

n.a. not applicable

[a] Represents clearance value in placebo arms, at -2–0 h prior to perpetrator administration, and the time intervals of efavirenz (6, 8] h and rifampicin [0, 22) h.

Red colored rows represent time intervals of maximum change in midazolam clearance per perpetrator arm.

Shaded grey rows represent the first time interval at which midazolam clearance significantly deviated beyond the boundary of 80%–125%. Grey boxes include all time intervals outside the bioequivalence limit.