

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