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An open-label study in healthy volunteers to evaluate the potential for cytochrome P450 3A4 inhibition by F901318 using oral midazolam as a probe

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Background: F901318 a novel orotomide antifungal is currently entering late-stage clinical development for invasive aspergillosis and invasive scedosporiosis. Here we evaluate its in vivo CYP3A4 inhibitory activity in healthy volunteers in a midazolam interaction study.

Material/methods: In an open label study midazolam (dose 2 mg orally) was dosed on Day 1 and again (on Day 7) after volunteers had been dosed with intravenous F901318 4 mg/kg bid for one day followed by 2.5 mg/kg bid for 7 doses to come to steady state.
Twenty subjects were entered into the study in two cohorts. The first cohort consisted of 12 subjects studied in two groups of six subjects each. This cohort was designed to test if there was a clear difference in midazolam kinetics detectable between the first dose and at F901318 steady state. If not then a second cohort of eight subjects would also be studied to define the magnitude of the difference.
PK sampling for midazolam and 1- and 4-hydroxy-midazolam plasma concentrations continued for up to and including 24 hours after dosing with midazolam on both occasions. PK sampling for F901318 continued from before the first dose and up to 24 hours after the ninth dose.

Results: The concentration-time profiles for midazolam in all 20 volunteers before and after iv dosing with F901318 are shown in Figure 1. The plasma exposures of midazolam and its 1-OH and 4-OH metabolites before and after iv F901318 dosing are summarised in Table 1. A small uplift was evident in C_{max} and AUC_{0-t} ratios (mean values of 1.27 and 1.65, respectively) indicating a minor interaction between F901318 and Midazolam. This minor interaction was also evident in small changes in mean C_{max} and AUC_{0-t} ratios for the 1- and 4-OH Midazolam metabolites.

Figure 1. Midazolam plasma concentration profiles on day 1 and day 7

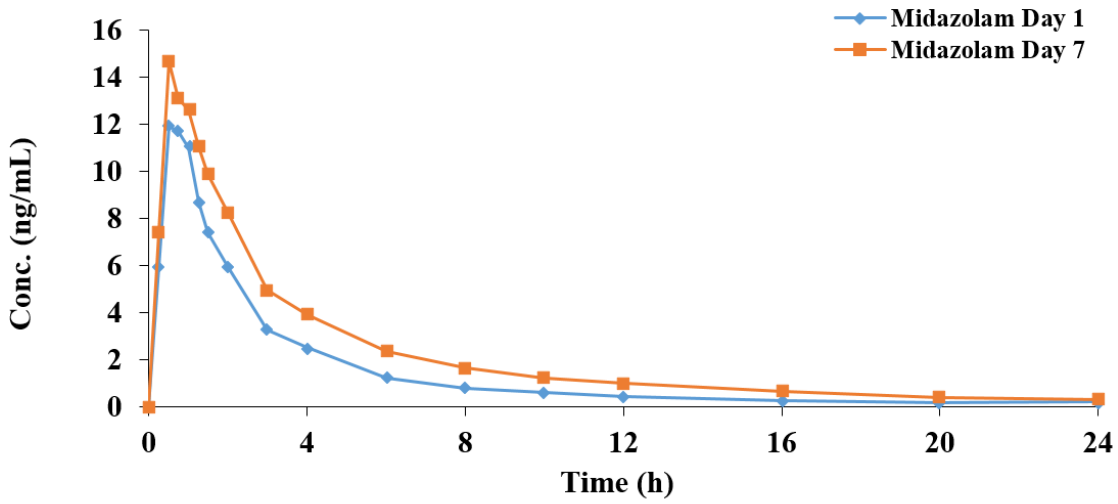

Table 1. Midazolam and its hydroxy metabolites exposures on day 1 and day 7

Day	Midazolam AUC_{0-t} (ng.h/mL)	Midazolam Cmax (ng/ml)	1-OH Midazolam AUC_{0-t}	1-OH Midazolam Cmax	4-OH Midazolam AUC_{0-t}	4-OH Midazolam Cmax
Day 1	34.25	13.8	10.6	4.91	1.11	0.51
	(±8.5)	(±4.3)	(±4.5)	(±2.4)	(±0.3)	(±0.1)
Day 7	53.36	16.7	9.82	3.82	1.69	0.59
	(±14.7)	(±4.8)	(±4.1)	(±1.9)	(±0.4)	(±0.1)
Ratio D7/D1	1.65 (±0.6)	1.27 (±0.4)	0.96 (±0.3)	0.81 (±0.3)	1.57 (±0.4)	1.18 (±0.2)

Values in parentheses are ± standard deviation

Conclusions: The small uplift in midazolam exposure after dosing volunteers with a F901318 loading and maintenance regimen categorises F901318 as a weak inhibitor of Cyp3A4 in man.