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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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Abstract

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.

Materials/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 one group of four subjects, followed by one group of eight subjects. This cohort was designed to test if there was a clear difference in midazolam kinetics detectable between the first and second doses of midazolam. 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 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 (geometric mean ratio values of 1.20 and 1.54, 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.

Conclusion:
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.

Introduction

F901318, also known as 2-(1, 5-dimethyl-3-phenyl-1H-pyrrol-2-yl)-N-[4-[4-(5-fluoro-pyrimidin-2-yl) piperazin-1-yl]-phenyl]-2-oxo-acetamide, is a fungal pyrimidine biosynthesis inhibitor, which is currently being developed by F2G Limited for the treatment of invasive fungal disease (IFD), particularly Invasive Aspergillosis (IA) and Invasive Scedosporiosis (IS). F901318 is the first of a new class of antifungal agents, the orotomides, and acts through the direct, competitive, and highly selective inhibition of dihydroorotate dehydrogenase (DHODH).

F901318 will be developed as an intravenous (IV) and oral (PO) treatment for IFD (IA, IS, and other rare mould infections). It shows excellent in vitro activity against both groups of fungi (as well as others). In vivo pharmacodynamic studies indicate that F901318 has better activity than current agents against *Aspergillus* spp., when the dosing regimen achieves trough plasma levels of ≥ 0.5 mg/L (*See abstract #2519, Hope et al*).

In vitro studies have revealed that F901318 is an inhibitor of CY3A4, with IC_{50} levels approaching the upper therapeutic range being targeted in man. As the target patient population are frequently receiving multiple medications, assessing the in vivo CYP3A4 inhibitory activity of F901318 at an early stage of the development program will help guide concomitant medication restrictions and/or dosage adjustments for future trials.

Methods

A total of 20 healthy male subjects, aged 18 to 45 years and weighing between 60 to 100 kg were dosed in 2 cohorts; both cohorts underwent the same dosing schedules of midazolam and F901318, and the same procedures. Cohort 1 consisted of 12 subjects, studied in 1 group of 4 and 1 group of 8 subjects. Cohort 2 (8 subjects) was dosed to give a definitive result, as there was no clear difference in midazolam kinetics detectable between the first and second doses of midazolam in Cohort 1. Doses were administered as follows, with each F901318 dose comprising a 4 hour intravenous infusion:

- Day 1: a single oral dose of 2 mg midazolam
- Day 3: 4 mg/kg F901318 bid IV
- Days 4 to 6: 2.5 mg/kg F901318 bid IV
- Day 7: a single oral dose of 2 mg midazolam and 2.5 mg/kg F901318 IV (9^{th} and final dose)

Validated LC-MSMS assays were used to measure midazolam, its major metabolites (1- and 4-OH midazolam) and F901318 in plasma.

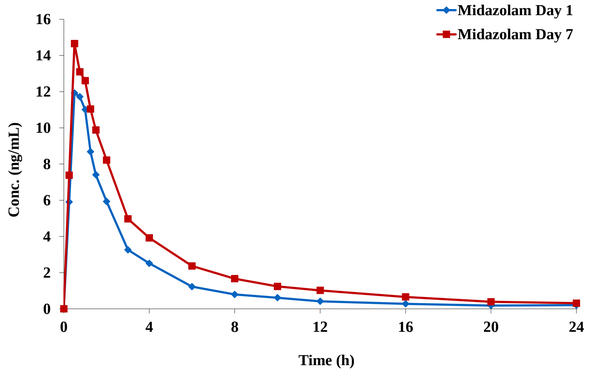
Results

Safety and Tolerability Results

- F901318 had an acceptable safety profile when administered twice daily for 5 days; there were no clinically significant changes in vital signs, 12-lead ECGs, laboratory tests or physical examinations.
- All Treatment Emergent Adverse Events (TEAEs) were mild or moderate in severity and there were no Serious Adverse Events. Infusion site reactions (including phlebitis pain and erythema; reported by 18 subjects) and dizziness (reported by 6 subjects) were the most frequently reported F901318-related TEAEs.
- The safety and tolerability profile was similar to that observed for the same dosing regimen but shorter infusion durations *(see poster 1711, Kennedy et al).*

Pharmacokinetic Results

Figure 1: Mean comparative midazolam plasma concentration-time plot (Days 1 and 7)



- When midazolam was co-administered with F901318, a small increase in midazolam systemic exposure was observed.
- Corresponding increases in C_{max} and AUC_{0-t} were observed for 4-OH midazolam, with slight decreases observed for 1-OH midazolam.
- The estimation of midazolam t½ showed a slight increase when co-administered with F901318, with mean (CV%) values of 4.6 h (31.8%) and 5.3 h (27.5%) on Days 1 and 7, respectively.
- F901318 reached steady state on Day 2, within 36 h of the first dose.

Table 1: Arithmetic Mean (CV%) Exposures of Midazolam and its Hydroxy Metabolites on Days 1 and 7

	Midazolam		1-OH midazolam		4-OH midazolam	
	AUC_{0-t} (ng.h/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	C_{max} (ng/mL)
Day 1	34.25 (24.7%)	13.8 (31.2%)	10.6 (42.6%)	4.91 (48.1%)	1.11 (23.6%)	0.51 (29.0%)
Day 7	53.36 (27.6%)	16.7 (28.5%)	9.82 (41.8%)	3.82 (49.7%)	1.69 (21.4%)	0.59 (18.1%)
Ratio of Geometric Means (90% CI)	**1.54** (1.31, 1.80)	**1.20** (1.05, 1.38)	**0.90** (0.75, 1.07)	**0.77** (0.66, 0.88)	**1.52** (1.37, 1.69)	**1.16** (1.07, 1.25)

Conclusion

- Intravenous infusions of F901318 at a loading dose of 4 mg/kg bid for 1 day followed by 4 days of maintenance dose at 2.5 mg/kg bid were shown to be safe in healthy volunteers, with an acceptable tolerability profile, as assessed in over 50 subjects.
- Although a small increase in midazolam systemic exposure was seen when midazolam was given concomitantly with F901318, the magnitude of change (1.25 - 2 fold) classes F901318 as a weak CYP3A4 inhibitor.
- As polypharmacy is frequently seen in IA patients, F901318 being a weak CYYP3A4 inhibitor is a favourable profile to that seen for the azoles, which are mainly classified as moderate or strong inhibitors of CYP3A4.