An Open Label Study to Evaluate the Potential for Cytochrome P450 3A4 Inhibition by F901318 using Oral Midazolam as a Probe

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Background
F901318 is a novel oxazole antifungal is currently entering late stage clinical development for invasive aspergillosis and invasive mould infections. Here we evaluate its in vivo CY34A3 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 at 1 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 whether there was a clear difference in midazolam kinetics detectable between the first and second doses of midazolam. If not, 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-hydroxymidazolam plasma concentrations continued for up to 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- and 4-hydroxymetabolites before and after F901318 dosing are summarised in Table 1. A small shift was evident in Cmax and AUC/0-24h 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 Cmin and AUC0-24h ratios for the 1- and 4-OH-Midazolam metabolites.

Conclusion
The small shift in midazolam exposure after dosing volunteers with a F901318 loading and maintenance regimen categories F901318 as a weak inhibitor of CY34A3 in man.

Abstract

Introduction

Safety and Tolerability Results

- F901318 had an acceptable safety profile when administered twice for 5 days; there were no clinically significant changes in vital signs, 12-lead ECG, 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 itching, pain and erythema; reported by 18 subjects) and dizziness reported by 5 subjects) were the most frequently reported F901318 related TEAEs.
- The safety and tolerability profile was similar to that observed for the standard antifungal regimen but shorter infusion durations (see poster 1711, Hannay et al).

Pharmacokinetic Results

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

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

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 schedule 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 dosing comprising a 4 hour infusion.

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

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

Conclusion

- When midazolam was co-administered with F901318, a small increase in midazolam systemic exposure was observed.
- Corresponding increases in Cmax and AUC0-24h were observed for 4-OH-Midazolam, with slight increases for 1-OH-midazolam.
- The estimation of midazolam t1/2 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.

- 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 the change (1.25 - 2 fold) classifies F901318 as unlikely to affect the antifungal exposure.
- A polymorphism is frequently seen in UK patients. F901318 being a weak CY34A3 inhibitor is a favourable profile to see that the azoles, which are mainly classified as moderate or strong inhibitors of CY34A4.