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Assessment of the duration of infusion on the tolerability and repeat dose pharmacokinetics of F901318 in healthy volunteers

Tony Kennedy[1], Graham Allen[2], Jan Steiner[3] , Markus Heep[1], Michael Birch[1]

[1] F2G Ltd, Eccles, United Kingdom, [2] Gamms Consultancy, Ancaster, United Kingdom, [3] Oxford Therapeutics Consulting, Bracknell, United Kingdom

Abstract

Background:
F901318 is in clinical development for treatment of invasive aspergillosis and scedosporiosis. Dosed over 4 hours, a loading regimen (4 mg/kg bid on day 1) followed by a maintenance dose (2.5 mg/kg bid) achieved the target steady state plasma concentrations predicted for efficacy. The current study investigated the safety tolerability and pharmacokinetic profiles of shorter dosing regimens.
Materials/methods:
Subjects between 18 and 45 years of age and weighing 60-100 kg were enrolled. The loading regimen was 4 mg/kg bid on Day 1 with seven maintenance doses of 2.5 mg/kg given bid over either 3, 2 or 1 hours. Cohorts of eight subjects were infused with placebo (2) or F901318 (6). For the 1 hour infusion cohort the loading doses were given over 2 hours and the maintenance dose given over 1 hour. F901318 pharmacokinetic profiles were generated on Days 1 and 5 by a validated LC-MS/MS assay.
Results:
The safety and tolerability profile was unchanged with similar incidence and pattern of adverse effects in all cohorts. The target exposure for efficacy (mean C_{min} of 0.5 µg/mL) was achieved in all cohorts and the plasma concentration profiles were essentially superimposable, regardless of infusion duration.
Conclusion:
Shorter infusion options are an important compliance and convenience factor. The F901318 infusion duration can be safely reduced to 1 hour without significantly increasing C_{max} and still achieving the target C_{min} for clinical efficacy.

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 indicated that F901318 had better activity than current agents against *Aspergillus* spp., when the dosing regimen achieved trough plasma levels of ≥0.5 mg/L (*See abstract #2519, Hope et al*).
Here we present Phase 1 study results aiming at establishing an IV dosing regimen for treatment of invasive aspergillosis in humans.

Methods

F901318 intravenous infusions were prepared from a stock solution containing F901318 (4 mg/mL); hydroxypropyl-β-cyclodextrin (250 mg/mL); polyethylene glycol (280 mg/mL) and polyvinyl pyrrolidone (10 mg/mL). Placebo comprised 0.9% w/v sodium chloride. The IV infusion was tested in a randomised, double-blind, placebo-controlled, sequential design study, with 6 subjects in each cohort receiving active compound and 2 subjects receiving placebo.

Healthy males between 18 and 45 years of age were entered into the study and were dosed for 5 days with F901318. Day 1 comprised a loading dose of 4 mg/kg bid and Days 2 to 5 comprised a maintenance dose of 2.5 mg/kg bid. Infusion durations of 3, 2 and 1 hour were sequentially evaluated across the 3 cohorts, with the 1 hour infusion cohort receiving the loading doses over 2 hours and the maintenance doses over 1 hour.

A validated LC MS/MS assay was used to measure F901318 in plasma.

Results

Safety and Tolerability Results

Multiple doses of F901318 when administered by iv infusion as a 1 day loading dose of 4 mg/kg bid followed by 4 days of maintenance dose of 2.5 mg/kg bid had an:

Acceptable safety profile .

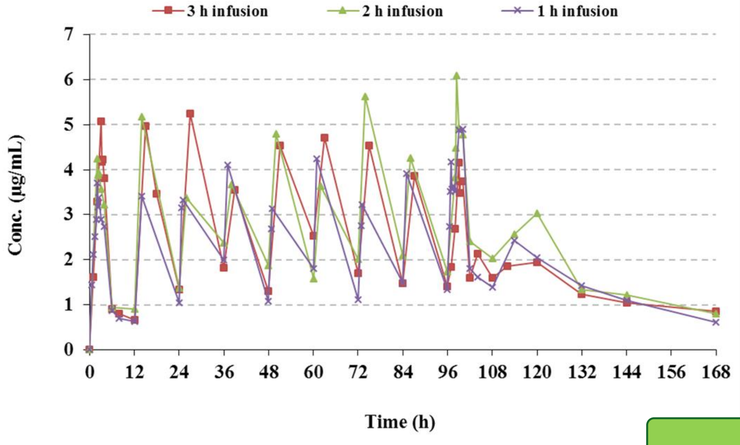
- There were no clinically significant changes that could reasonably be attributable to F901318 in vital signs, 12-lead ECGs, laboratory variables, or physical examinations.

Acceptable tolerability profile

- All Treatment Emergent Adverse Events were of mild or moderate intensity, and there were no Serious Adverse Events.
- Infusion site reactions and dizziness were the most commonly reported adverse events. Across all 3 cohorts, infusion site pain and infusion site phlebitis were reported in 44% and 39% of subjects who received F901318, respectively, compared to 17% of subjects who received placebo. Dizziness was reported by 67% of subjects who received F901318, and 17% who received placebo.
- Infusion duration did not adversely impact the frequency or severity of treatment related adverse events.

Pharmacokinetic Results

Figure 1: Mean plots of 4 mg/kg bid (Day 1) then 2.5 mg/kg bid
(given as 1, 2 and 3 h infusions)



Regimens tested at 4 mg/kg 2 x daily for 1-day then 2.5 mg/kg 2 x daily			
Infusion duration (h)	**Study Day**	**Mean C_{max} (µg/mL)** *[range]*	**Mean C_{12} (µg/mL)** *[range]*
3	1	**5.07** *[3.36 - 5.88]*	**0.66** *[0.47 - 0.89]*
	5	**4.44** *[3.47 - 6.36]*	**1.60** *[0.82 - 3.31]*
2	1	**4.51** *[3.77 - 5.97]*	**0.87** *[0.56 - 1.47]*
	5	**6.55** *[4.49 - 7.93]*	**2.03** *[1.63 - 2.80]*
1	1	**3.97** *[2.86 – 5.90]*	**0.63** *[0.37 – 1.02]*
	5	**5.83** *[3.25 – 8.85]*	**1.39** *[0.77 – 2.12]*

- By using a loading dose of 4 mg/kg bid iv, followed by a maintenance dose of 2.5 mg/kg bid iv, steady state was reached within 24 h, with mean accumulation ranging from 1.3- to 1.8-fold.
- Trough levels (C_{12}) were ≥ 0.7 µg/mL in all subjects by Day 2, with mean values on Day 5 ranging from 1.3 to 2 µg/mL.
- Infusion duration had no impact upon concentration:time plots, with similar peak and trough values being seen for the 1, 2 and 3 h infusions.
- The PK profile seen was indicative of a rapid bi-exponential decline, which, together with a volume of distribution of ca. 3 L/kg, suggests that F901318 is extensively distributed into highly perfused tissues.
- Terminal elimination half-life was estimated to be ca. 20 to 30 hours. However, determination of this parameter was perturbed by the secondary peaks observed in most subjects, which are most likely due to enterohepatic recirculation.

Conclusion

- Multiple iv infusions (1 to 3 h duration) of F901318, when given to healthy volunteers as a loading dose of 4 mg/kg bid for 1 day followed by a maintenance dose of 2.5 mg/kg bid for 4 days, were safe, with an acceptable tolerability profile.
- With this dosing regimen plasma levels quickly exceeded the drug exposures required for efficacy in IA animal models.
- Individual subject trough levels (C_{12}) of ≥ 0.7µg/mL were attained within 24 h of the first dose, regardless of infusion duration.
- Faster infusions did not have any impact upon C_{max}, thereby indicating that F901318 maintenance infusion duration can be safely reduced to one hour.