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Multiple Dose Pharmacokinetics of an Immediate-Release Tablet Formulation of F901318 in Healthy Male and Female Subjects

Tony Kennedy[1], Graham Allen[2], Jan Steiner[3], Markus Heep[1], Jason Oliver[1], Graham Sibley[1], Derek Law[1]

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

Abstract

Background:
F901318 is a novel orotomide antifungal agent being developed for the treatment of invasive aspergillosis and scedosporiosis. An oral immediate release tablet developed to support long term treatment in patients has been evaluated in a Phase 1 repeat dose study.
Materials/methods
F901318 tablets (120 mg active) were made with a hypromellose acetate succinate based formulation. The tablets were tested in a double blind placebo controlled, randomised, parallel group study in 10 healthy male and female subjects, 8 taking active compound and 2 taking placebo.
Healthy males or females between 18 and 55 years of age and weighing between 50-100 kg were entered into the study and were dosed for 10 days once daily with three F901318 tablets (360 mg OD). A validated analytical assay was used to measure F901318.
Results
F901318 was well tolerated in the study with only mild or moderate adverse events observed.
The key pharmacokinetic parameters T_{max}, C_{max}, AUC_{0-12}, AUC_{0-24} and AUC_{0-t} are summarised in Table 1. Evidence of enterohepatic recirculation was seen in the presence of secondary peaks which precluded estimation of t½. The plasma F901318 profiles were generally similar between volunteers and exhibited accumulation with C_{max} and AUC0-24 values on day 10 about 2.5 fold and 3.9 fold higher than on day 1. The mean C_{24} results show that on Day 1 the C_{min} level was ca. 0.5 µg/mL and by Day 10 was 1.8 µg/mL. Inspection of the mean full profile plot shows that from Day 3 onwards the mean C_{min} values were consistently in the range of ca. 1 to >2 µg/mL surpassing F901318 exposures needed for efficacy in animal models.
Conclusion
F901318 dosed once daily to healthy volunteers at a dose of 360 mg for ten days was well tolerated. Plasma exposure levels were achieved which exceed the drug exposures required for efficacy in animal models of invasive aspergillosis.

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*).
Here we present Phase 1 study results evaluating the oral dosing regimen required to support long term use in patients.

Methods

F901318 Immediate Release (IR) tablets (120 mg active) were made with a hypromellose acetate succinate based formulation. The tablets were tested in a double blind placebo controlled, randomised, parallel group study in 10 healthy male and female subjects, 8 (4 male, 4 female) taking active compound and 2 (1 male, 1 female) taking placebo.
Healthy subjects between 18 and 55 years of age and weighing between 50-100 kg were entered into the study and were dosed for 10 days once daily with three F901318 tablets (360 mg OD). Each dose was given after an overnight fast, with no food permitted until 2 h post-dose.
A validated analytical assay was used to measure F901318 in plasma.

Results

Safety and Tolerability Results

- 360 mg F901318 was well tolerated when administered orally QD for 10 days in the fasted state. No deaths, severe adverse events (AE)s or Serious AEs were reported, and no subject was withdrawn as a result of an AE. The majority of AEs reported following dosing with F901318 were mild in severity.
- Following dosing with F901318, 50% subjects reported a total of 5 IMP-related AEs: 2 subjects with increased ALT, 1 subject with both diarrhoea and nausea, and 1 subject with dizziness.
- With exception of 2 mild AEs of increased ALT, no subject had clinically significant safety laboratory variables, vital signs or ECG findings..

Pharmacokinetic Results

- Following multiple oral dosing of 360 mg F901318 QD, steady state was reached within 3 days of dosing, where systemic exposure (based upon C_{max} and AUC_{0-24}) was 2.5 and 3.9-fold higher respectively than that seen on Day 1.
- Once steady state was attained, the once daily regimen gave trough level (C_{24}) values in excess of 0.7 µg/mL for all subjects, with mean levels consistently falling between 1 and 2 µg/mL.
- Secondary peaks were observed in the elimination phase of the plasma concentration:time profiles for most subjects, which are likely attributable to enterohepatic recycling.

Figure 1. F901318 Mean plasma peak and trough concentrations during 10 day dosing

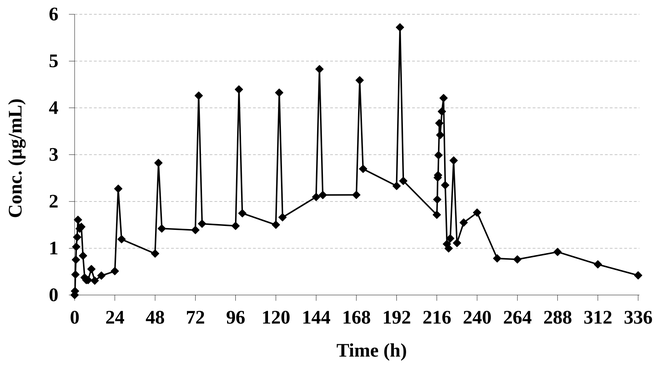
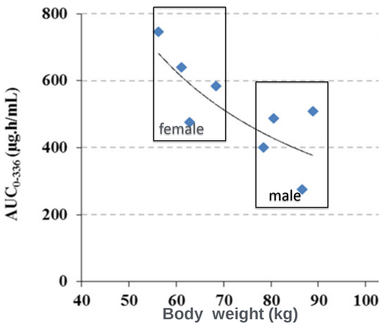


Table 1: Geometric Mean (Geometric CV%) Plasma Pharmacokinetic Parameters for F901318
following 360 mg F901318 IR Tablet (3 × 120 mg) QD for 10 Days in the Fasted State

	All Subjects N = 8		Male Subjects N = 4		Female Subjects N = 4	
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
C_{max} (µg/mL)	1.78 (72.3)	4.08 (59.2)	1.30 (99.7)	2.64 (41.1)	2.44 (16.3)	6.31 (19.6)
T_{max}[a] (h)	2.0 (1.5-5.0)	3.5 (1.0 - 16.0	2.0 (1.5-5.0)	2.75 (1.0-16.0)	2.5 (2.0-4.0)	3.5 (1.5-4.0)
C_{24} (µg/mL)	0.435 (77.5)	1.64 (44.1)	0.318 (102.4)	1.34 (42.1)	0.594 (35.5)	2.00 (39.2)
$AUC_{(0-24)}$ (µg.h/mL)	12.5 (61.9)	44.5 (40.4)	9.87 (80.7)	35.6 (40.0)	15.8 (33.7)	55.5 (27.6)

- The higher systemic exposure for F901318 observed in females appears to be linked to body weight, as seen in Figure 2 (r^2 value = 0.54). .
- The apparent gender differences in systemic exposure of F901318 seen in this study (where the cohort size is very small) have not been seen with single doses of F901318.
- The safety and tolerability findings following 360 mg qd for 10 days were independent of gender.

Figure 2: AUC_{0-336} versus bodyweight



Conclusion

- F901318 administered once daily to healthy volunteers at a dose of 360 mg qd for ten days was safe and well tolerated.
- Trough plasma levels of F901318 were achieved in all subjects which exceeded the drug exposures required for efficacy in animal models of IA.
- The potential for gender and/or body weight differences will be monitored throughout the clinical development program.
- The data are highly supportive of an oral dosing regimen for long term use in the clinical setting.