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Pharmacokinetics of F901318 in man from an Intravenous Single Ascending Dose Study.

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Abstract

Background: F901318 is the first member of the orotomide class of antifungal agents acting via inhibition of DHODH a key enzyme in pyrimidine biosynthesis. Excellent *in vivo* efficacy has been demonstrated in murine infection models together with good pharmacokinetics, tissue distribution and oral bioavailability. F901318 is currently being developed as an IV and oral agent for the treatment of invasive aspergillosis. Here we present data on the Phase I IV single ascending dose study in man.
Methods: Healthy male volunteers aged between 18 and 45 years and weighing 60 - 90 kg, were dosed with F901318 or placebo as 4 h intravenous infusions. Salient PK parameters were calculated using non-compartmental analysis.
Results: The plasma profiles (n=6/dose level) exhibited a typical increase to a C_{max} value at or near the end of infusion before declining in a biphasic manner over the remaining sampling time (120 h in total). The terminal elimination $t_{1/2}$ was 30 h at the 4 mg/kg dose. The majority of the exposure was accounted for, during the 120 h period post start of dosing, as the extrapolated percentages of AUC from time t to infinity were generally < 5 %. The rapid plasma clearance and high volume of distribution indicated that F901318 rapidly distributed into highly perfused tissues. A decrease in CL values was noted as doses were escalated, consistent with a $t_{1/2}$ increase, but indicated a levelling off at the 3 and 4 mg/kg levels. The mean C_{max} and $AUC_{0\text{-}t}$ values across the entire dose range were only slightly higher than dose proportional. Less than 0.2% of the total dose was recovered in urine as F901318. Overall, F901318 was well tolerated across the dose range of 0.25 to 4 mg/kg with no adverse events observed.

Mean (n=6/dose) pharmacokinetic results for F901318 from an intravenous SAD study

Dose (mg/kg)	C_{max} (µg/mL)	$AUC_{0\text{-}t}$ (µg.h/mL)	$AUC_{0\text{-}\infty}$ (µg.h/mL)	$t_{1/2}$ (h)	CL (mL/h)/kg	V_{ss} (mL)/kg
0.25	0.172 (36.5)*	1.30 (58.6)	1.31 (58.6)	15.2 (23.5)	235.9 (42.5)	3002 (19.3)
0.75	0.550 (18.2)	4.02 (17.9)	4.09 (18.0)	21.9 (42.5)	188.1 (16.9)	3494 (41.5)
1.5	1.171 (25.1)	12.68 (27.4)	13.07 (26.9)	25.1 (21.9)	121.0 (23.9)	3342 (23.1)
3.0	2.74 (19.0)	29.92 (25.7)	28.78 (22.7)	23.9 (37.8)	108.7 (22.7)	2893 (32.0)
4.0	3.26 (24.6)	38.04 (30.3)	40.94 (34.0)	30.2 (33.1)	110.5 (43.1)	3198 (12.2)

Conclusion: F901318 demonstrated predictable and linear single dose pharmacokinetics over the studied dose range of 0.25mg/kg-4mg/kg and combined with its excellent safety profile warrants progression into further clinical studies.

Introduction

Currently there are limited options for the treatment of serious systemic fungal disease. The three existing classes of antifungal drugs were introduced many years ago and the discovery of new agents with distinctive mechanisms of action has proved to be challenging as drug selectivity for fungal targets proved elusive. Limitations to the use of existing agents include drug toxicities, variability in drug handling, drug interaction liabilities and increasing incidence of resistance.
F901318 is a novel agent of a new orotomide class of antifungals discovered by whole cell screening and whose mechanism of action has been characterised. Excellent *in vivo* efficacy has been demonstrated in murine models of invasive aspergillosis together with good pharmacokinetics, tissue distribution and oral bioavailability Preclinical safety and efficacy studies have supported the progression of F901318 into Phase 1 clinical trials which initially are evaluating the intravenous formulation. The first in man single ascending dose study has now been completed and the pharmacokinetic results from the study are reported.

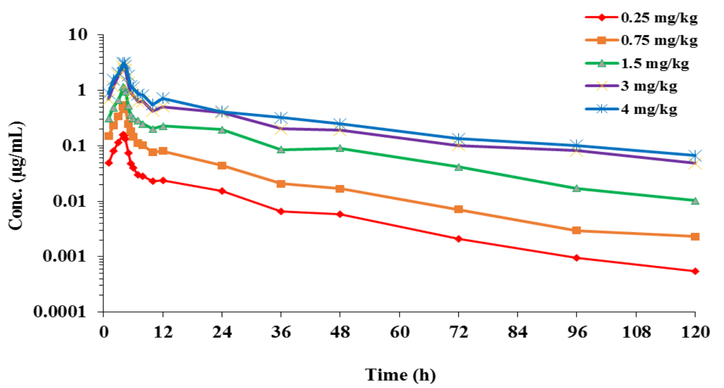
Methods

Healthy male volunteers aged 18 to 45 years and weighing 60 - 90 kg were dosed with F901318 formulated in a beta-hydroxypropyl cyclodextrin vehicle or placebo as 4-h IV infusions. The validation ranges for the determination of F901318 in human plasma were 0.1 to 50 ng/mL and 10 to 5000 ng/mL (using a D_8 internal standard). For both plasma and urine, F901318 was extracted using a liquid-liquid system prior to reconstitution and analysis by LC-MS/MS (linear calibration lines). Validation of precision, accuracy, selectivity, matrix effects, stability, dilution and carryover were successfully carried out for both methods. PK parameters were calculated using non-compartmental analysis (1).

Results

The plasma profiles (n=6/dose level) are shown in Figure 1 for 0-120 hr and in Figure 2 for 0-12 hr. Plasma concentrations exhibited a typical increase to a C_{max} value at or near the end of infusion before declining in a biphasic manner over the remaining sampling time (120 h in total). Pharmacokinetic parameters are summarised in Table 1. The terminal elimination $t_{1/2}$ was 30 h at the 4 mg/kg dose. The majority (>95%) of the exposure was accounted for during the 120 h period post start of dosing. The rapid plasma clearance and high volume of distribution indicated that F901318 rapidly distributed into highly perfused tissues. A decrease in CL values was noted as doses were escalated, consistent with a $t_{1/2}$ increase, but indicated a levelling off at the 3 and 4 mg/kg levels. Proportionality of the mean C_{max} and $AUC_{0\text{-}t}$ values to dose are displayed in Figures 3 and 4. Across the entire dose range these parameters were only slightly higher than dose proportional. Less than 0.2% of the total dose was recovered in urine as parent compound. F901318 was well tolerated across the dose range of 0.25 to 4 mg/kg with no adverse events of concern observed.

Figs. 1 and 2 Mean (n=6/dose) concentration-time profiles for F901318 after single intravenous dose ranging from 0.25 to 4 mg/kg to healthy male volunteers



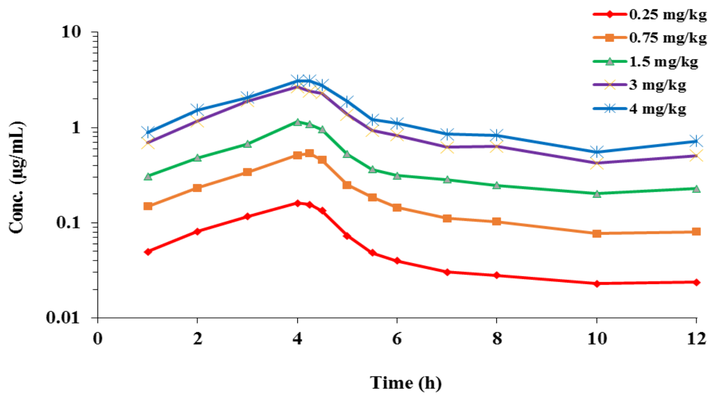


Table 1

Dose (mg/kg)	C_{max} (µg/mL)	$AUC_{0\text{-}t}$ (µg.h/mL)	$AUC_{0\text{-}\infty}$ (µg.h/mL)	$t_{1/2}$ (h)	CL (mL/h)/kg	V_{ss} (mL)/kg
0.25	0.172 (36.5)*	1.30 (58.6)	1.31 (58.6)	15.2 (23.5)	235.9 (42.5)	3002 (19.3)
0.75	0.550 (18.2)	4.02 (17.9)	4.09 (18.0)	21.9 (42.5)	188.1 (16.9)	3494 (41.5)
1.5	1.171 (25.1)	12.68 (27.4)	13.07 (26.9)	25.1 (21.9)	121.0 (23.9)	3342 (23.1)
3.0	2.74 (19.0)	29.92 (25.7)	28.78 (22.7)	23.9 (37.8)	108.7 (22.7)	2893 (32.0)
4.0	3.26 (24.6)	38.04 (30.3)	40.94 (34.0)	30.2 (33.1)	110.5 (43.1)	3198 (12.2)

Fig. 3 Dose vs Cmax plot

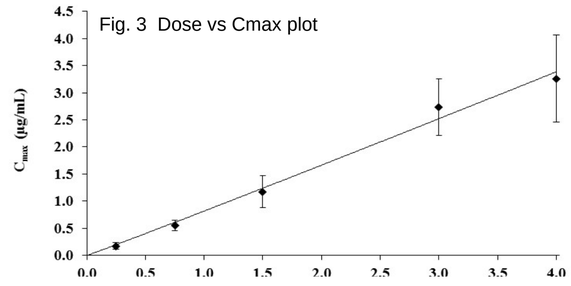
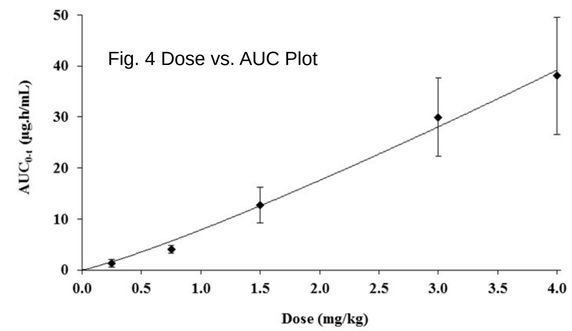


Fig. 4 Dose vs. AUC Plot



Conclusions

F901318 demonstrated predictable and linear single dose pharmacokinetics over the dose range of 0.25 mg/kg-4 mg/kg. The pharmacokinetic profile displayed by F901318 and the exposures achieved in this single dose intravenous study are in line with the preclinical PK scaling predictions and on target for PK/PD predicted efficacy exposures on repeat dosing. These PK results combined with an excellent safety profile warrant progression of F901318 into further clinical studies.

References

G.D. Allen, 'Modfit: a pharmacokinetics computer program' Biopharm. and Drug Disp., Vol. 11, 477-498, 1990