# Pharmacokinetics and Pharmacodynamics (PK-PD) of F901318 Against *Aspergillus fumigatus*

M-394

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## ABSTRACT

Background: F901318 is a novel mechanism of action antifungal agent with potent activity against *Aspergillus* spp. F901318 is in early stage clinical development. An understanding of the PK-PD of F901318 is required for selection of effective regimens for further study in phase II and III clinical trials.

Methods: A neutropenic murine model of invasive pulmonary aspergillosis was used for all experiments. The primary PD endpoint was serum galactomannan (GM). The relevant PK-PD index was determined using azole-susceptible and azole resistant strains as challenge organisms. The relationship between drug exposure and the impact of dose fractionation on GM, survival, and histopathology were determined. Results were benchmarked against a clinically relevant exposure of posaconazole.

Results: F901318 exhibited linear PK. A total daily dose of F901318 of 24 mg/kg was found to produce a good dynamic range of responses, with consistently better response with increasingly fractionated regimens: once daily dosing produced little effect but division into 3 doses produced maximal effect. Total plasma concentrations of F901318 were > MIC of the test organisms (0.03 mg/L for all isolates) for the dosing interval for all studied regimens. The ratio of the minimum total plasma concentration:MIC (Cmin:MIC) was the PD index that best linked drug exposure with observed effect. A Cmin and Cmin:MIC of 1 mg/L and 10-30, respectively, appear to be appropriate PD targets for F901318. The target is independent of azole susceptibility, and such exposures result in a greater decline in GM than are observed with clinically relevant exposures of posaconazole in this murine model. The pattern of maximal effect evident with these drug exposure targets was also apparent for survival and histopathological clearance.

Conclusions: F901318 exhibits time-dependent antifungal activity with the Cmin:MIC as the dynamically linked variable. A Cmin and Cmin:MIC of 1 and 10-30, respectively results in antifungal activity that exceeds that induced by posaconazole. The PK-PD of F901318 was the same for azole-susceptible and azole resistant strains, using a variety of endpoints. These results can now be used to select regimens for phase II and III clinical trials.

## BACKGROUND

- Invasive aspergillosis is a life threatening infection in immunocompromised hosts
- There are relatively few treatment options and no new anti-*Aspergillus* drug classes have been developed in the past 20 years
- F901318 has potent *in vitro* activity against *Aspergillus* spp. and has a novel mechanism of action
- PK-PD is required to identify the optimal dosage and schedule of administration that is likely to be associated for maximal antifungal activity

## METHODS

### EXPERIMENTAL MODEL

- A well-validated persistently neutropenic model of invasive pulmonary aspergillosis was used. Immunosuppression was induced with cyclophosphamide and cortisone acetate. Conidia were instilled into the nares, resulting in a lethal invasive pulmonary infection.

### PHARMACOKINETICS (PK) and PHARMACODYNAMICS (PD)

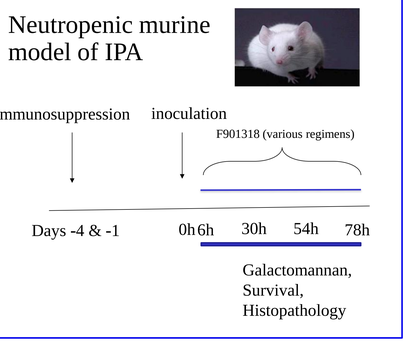
- Preliminary dose-finding studies were conducted to identify exposure-response relationships
- The primary model readout was circulating galactomannan concentrations
- Dose fractionation studies were conducted with the full dose administered q24h, two half dosages administered q12h, and three one-third dosages administered q8h.
- The plasma PK was defined. Plasma concentrations of F901318 were measured using LC/MS/MS
- Additional studies were performed using survival as an endpoint (3 days of treatment followed by observation)
- Histopathological changes in the lung were determined and sections were stained with GMS
- Posaconazole was used throughout as a positive control

### PK-PD MODELING

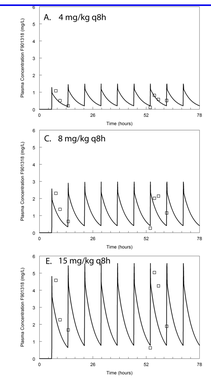
- A linked PK-PD mathematical model was fitted to the PK and PD dataset using a population methodology and the program Pmetrics
- The mathematical models were used to calculate the galactomannan at the end of the experiment and the area under the galactomannan-time curve
- A Kaplan Meir analysis was used to describe the survival data

## RESULTS

### 1. Experimental Design



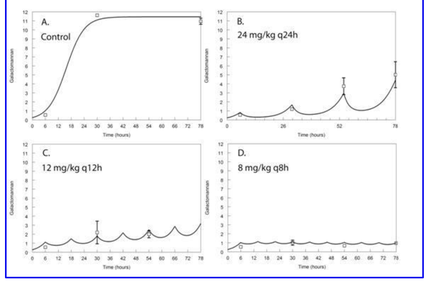

### 2. Murine Pharmacokinetics



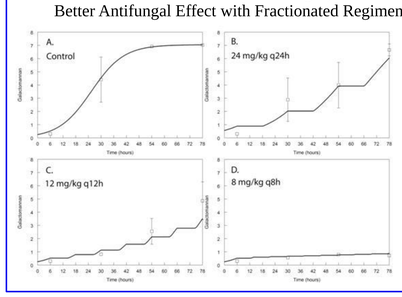

- PK linear with i.v. dosing
- $t_{1/2}$ 2.4 hours
- All regimens result in T>MIC 0.03 mg/L for 100% dosing interval

### 3. Dose Fractionation Studies

NIH/4215 Triazole Wild-Type: Better Antifungal Effect with Fractionated Regimen



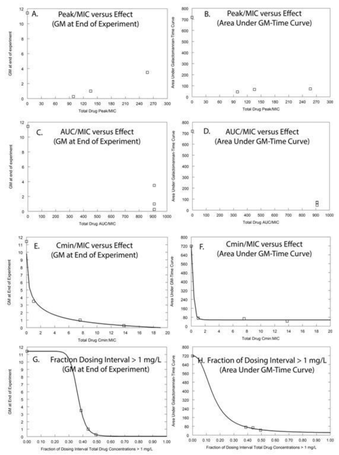

16216 Triazole L98H Mutant (Posaconazole MIC 0.25 mg/L): Better Antifungal Effect with Fractionated Regimen




NOTES on Transformation Studies

- Time-dependent antifungal activity evident
- But, T>MIC for all regimens & a range of protein binding estimates mean a different descriptor is required
- However, Cmin:MIC or T>MIC in presence of serum can both be used

NIH/4215 Transformation Studies: The Cmin:MIC or T>MIC in Presence of Serum are the Dynamically Linked Variables

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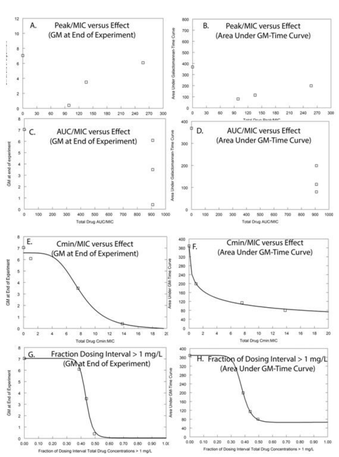
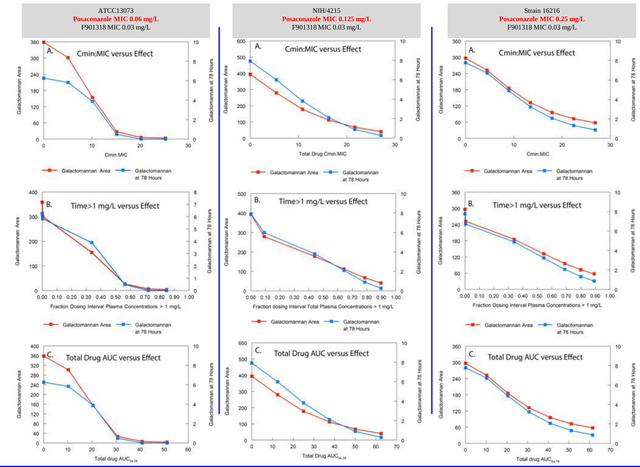


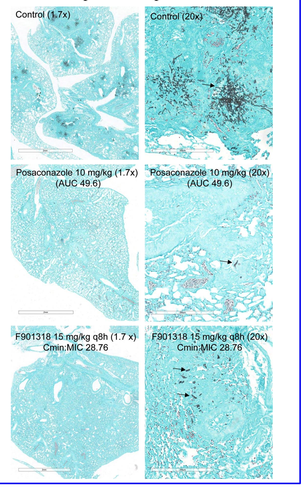

### 4. Exposure Response Relationships

F901318 induces an exposure-dependent decline in galactomannan regardless of the triazole genotype/phenotype. A clinically relevant exposure of posaconazole induces approx. 20% decline in galactomannan in this model




### 5. Histopathology

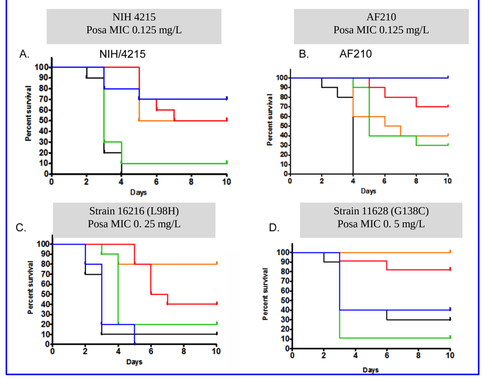
F901318 induces an improvement in histopathological appearances in the lung that are comparable to posaconazole




### 6. Survival

F901318 induces a drug exposure dependent prolongation of survival that is independent of triazole genotype/phenotype

Blue: posaconazole 10 mg/kg/day
Green: F901318 Cmin:MIC 1.13
Orange: F901318 Cmin:MIC 15.34
Red: F901318 Cmin:MIC 28.76
Black: Controls




## CONCLUSIONS

- F901318 demonstrates linear plasma PK
- F901318 causes a dose-dependent reduction in circulating galactomannan, prolongation of survival and improved histopathological appearances in the lung
- F901318 exhibits time-dependent antifungal activity
- The relevant dynamically linked variables are Cmin:MIC or T>MIC determined in the presence of serum
- In this severe model a Cmin:MIC of 10-30 results in near maximal reduction in galactomannan, and is equivalent to a Cmin of 1 mg/L