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O0940 The orotomide F901318 is efficacious in a murine model of Coccidioides meningitis

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Background: *Coccidioides* meningitis can lead to significant morbidity. F901318 is an advanced analog of the orotomide class of antifungal agents that inhibits fungal pyrimidine biosynthesis. Our objective was to evaluate the *in vitro* and *in vivo* activity of F901318 against *Coccidioides* species.

Materials/methods: *In vitro* activity of F901318 was assessed against 20 clinical isolates of *Coccidioides* species according to the CLSI M38-A2 standard. A *C. immitis* clinical isolate was used to establish infection in immunocompetent mice via intracranial inoculation with arthroconidia. Oral antifungal therapy began 48 hours post-inoculation and consisted of vehicle control, F901318 daily doses of 20 mg/kg (6.67 mg/kg TID or 10 mg/kg BID), and 40 mg/kg (13.3 mg/kg TID or 20 mg/kg BID), or fluconazole (25 mg/kg BID). Treatment continued for 7 and 14 days in the fungal burden and survival arms, respectively. Fungal burden was assessed by CFU counts in brain tissue.

Results: F901318 demonstrated potent *in vitro* activity (GM MIC of 0.015 mg/L; range $\leq$ 0.008 - 0.06 mg/L). Survival was significantly enhanced in mice treated with F901318 (median survival 22 - >30 days) compared to vehicle (9 days; $p < 0.0001$). Reductions in brain tissue fungal burden were also observed on day 9 in the F901318 groups (mean range 1.95 - 4.36 log CFU/g) compared to control (5.53 - 5.97 log CFU/g; $p \leq 0.01$). Improvements in survival and reductions in fungal burden also occurred with fluconazole. More frequent dosing of F901318 was also associated with enhanced survival and greater reductions in fungal burden. In the F901318 13.3 mg/kg TID group, fungal burden remained low (1.13 log CFU/g) on day 30, 15 days after treatment stopped, with 70% of mice having CFU counts below the limit of detection. In contrast, fungal burden rebounded in all other groups in the survival arm after therapy stopped.

Conclusions: F901318 was highly active *in vitro* and *in vivo* against *Coccidioides*. Significant improvements in both survival and fungal burden were observed in mice with coccidioidal meningitis and treated with F901318. Further studies are warranted to determine the clinical efficacy of F901318 in the treatment of coccidioidomycosis.