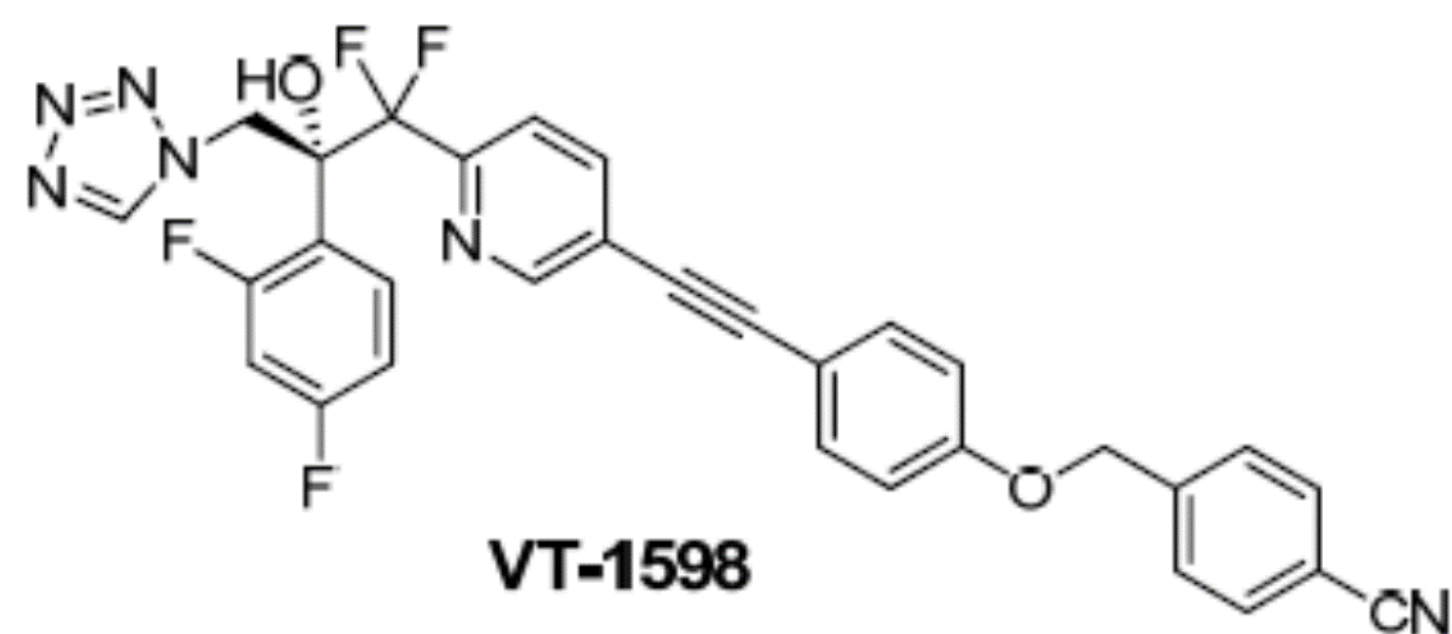


Intro and Objectives

Coccidioidomycosis (Valley Fever) is a major fungal infection in the southwestern U.S. Current therapy, especially for chronic infections, is limited by side effects, drug-drug interactions, and incomplete efficacy. VT-1598 is a novel antifungal with much improved selectivity for fungal CYP51 versus human CYP enzymes, a property that should yield a high therapeutic index. Its efficacy in a CNS coccidioidomycosis model has previously been described. We report here the activity of VT-1598 in treating respiratory coccidioidomycosis in mice.

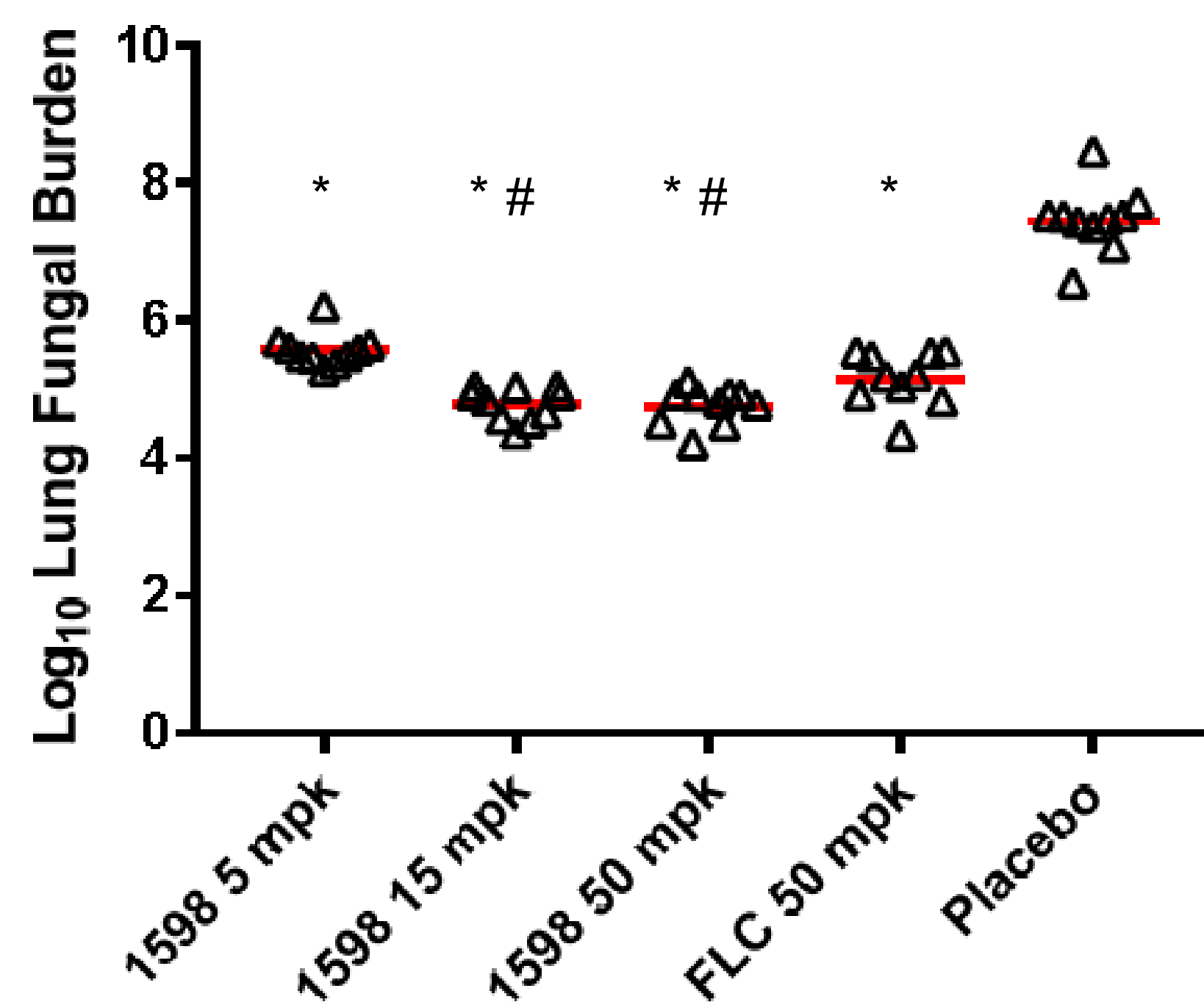


Materials & Methods

Five days after intranasal infection with a lethal dose of *C. posadasii* Silveira strain spores, oral treatment of once-daily 5, 15, and 50 mg/kg VT-1598, twice-daily 25 mg/kg (50 mg/kg/day) fluconazole (FLC), or vehicle control (20% cremophor EL) was administered to female Swiss-Webster mice (N=10/group) for 7 days. One day after the last dose, mice were euthanized, bled and weighed. Lungs were homogenized and colony-forming units enumerated (total lung fungal burden); spleen fungal growth was qualitatively assessed for dissemination. VT-1598 plasma levels were quantified by HPLC/MS/MS (OpAns, LCC, Durham, NC). Animal weights are reported as weight on day of sacrifice relative to day 1 weight.

Results

Figure 1: Lung Fungal Burden in a Murine Model of Respiratory Coccidioidomycosis



* P<0.001 vs. placebo. #P=0.02 vs. FLC

Table 1. Clinical and PK Observations from a Murine Model of Respiratory Coccidioidomycosis (1 day after last dose).

Treatment	Mean Weight Change ¹ (g)	Dissemination to Spleen (#)	Clinical State	Plasma Drug Level (µg/ml)
Placebo	-4.0	10	Morbid ²	-
FLC 50 mg/kg/d ³	-0.6	4	Healthy	N.D. ⁴
VT-1598 5 mg/kg	-0.4	7	Healthy	3.5
VT-1598 15 mg/kg	+1.0	0	Healthy	15
VT-1598 50 mg/kg	+2.1	0	Healthy	30

¹Body weight relative to day 1. ²Placebo mice were very ill at end of study; all were on supportive fluid therapy and 4/10 were sacrificed a day early. ³FLC dosed at 25 mg/kg twice-daily. VT-1598 dosed once-daily. ⁴Fluconazole levels were not determined in this study. Based on literature PK (Humphrey et al. AAC, 1985), it is estimated that FLC plasma level would be ~1.5 µg/ml 1 day after last dose.

Conclusions

- VT-1598 was highly efficacious as an oral treatment of murine respiratory coccidioidomycosis.
- Fungal burden reduction and clinical improvements were dose dependent in comparing VT-1598 low and mid doses, but were similar comparing the mid and high doses, suggesting the mid dose achieved maximal effect in this model.
- In comparing the mid VT-1598 dose with fluconazole, VT-1598 was superior in fungal burden reduction, prevention of dissemination, and mean weight differences at 1/3 the total daily dose.
- These data strongly support exploring VT-1598 in clinical studies of respiratory coccidioidomycosis.