Efficacy of the Novel Fungal Cyp51 Inhibitors VT-1161 and VT-1411 against Invasive Candidiasis Caused by *Candida albicans* and *Candida glabrata*

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BACKGROUND & OBJECTIVE

- *Candida* species are the fourth most common cause of nosocomial bloodstream infections in the U.S.
- *C. albicans* and *C. glabrata* are the two most common species associated with these infections.
- The clinical investigational agent VT-1161 and a next generation candidate VT-1411 are fungal Cyp51-selective inhibitors with potent in vitro activity against *Candida* species (Fothergill, ICAAC 2010, abstr. F-851 & ICAAC 2011, abstr. F-1381).
- Our objective was to evaluate the in vivo efficacy of these agents against invasive candidiasis caused by *C. albicans* and *C. glabrata*.

MATERIALS & METHODS

***Candida* Isolates**

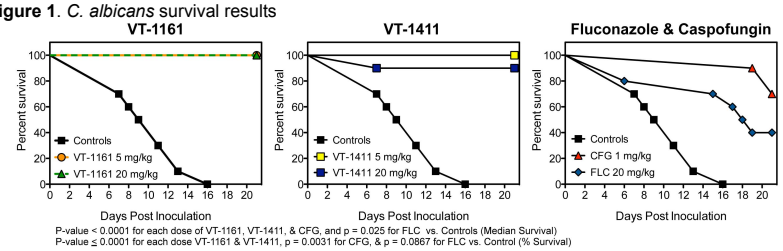
- *C. albicans* & *C. glabrata* clinical isolates ATCC 90028 and 05-761, respectively, were used.
- Isolates were subcultured twice on SDA plates and grown in brain heart infusion broth overnight prior to in vivo studies.

Murine Model of Invasive Candidiasis

- Outbred male ICR mice were used. Immunocompetent mice were infected with *C. albicans* while those infected with *C. glabrata* were rendered neutropenic (5-fluorouracil 150 mg/kg IV x 1 on the day prior to inoculation).
- Mice were infected intravenously via the lateral tail vein.
  - Target infecting inoculum
    - *C. albicans* ATCC 90028 - 1.5 x 10^6 cells/mouse
    - *C. glabrata* 05-761 – 1.0 x 10^8 cells/mouse
- Antifungal therapy began 1 day post-inoculation and consisted of the following (N = 10 mice per group per arm):
  - Placebo controls (0.5% carboxymethylcellulose PO QD)
  - VT-1161 5 & 20 mg/kg PO QD
  - VT-1411 5 & 20 mg/kg PO QD
  - Fluconazole 20 mg/kg PO QD
  - Caspofungin 1 mg/kg IP QD
- Survival and fungal burden were assessed
  - ***Survival arm*** – Therapy continued through day 7 and mice were monitored off therapy until day 21. Survival was assessed by Kaplan-Meier analysis.
  - ***Fungal burden arm*** – Therapy continued through day 7. Kidneys were collected on day 8. Fungal burden was assessed by colony-forming units (CFU/g tissue).
- Plasma was collected on day 8, and on the days that the mice succumbed to infection or day 21 in those infected with *C. albicans*. Plasma concentrations were measured by LC/MS-MS.

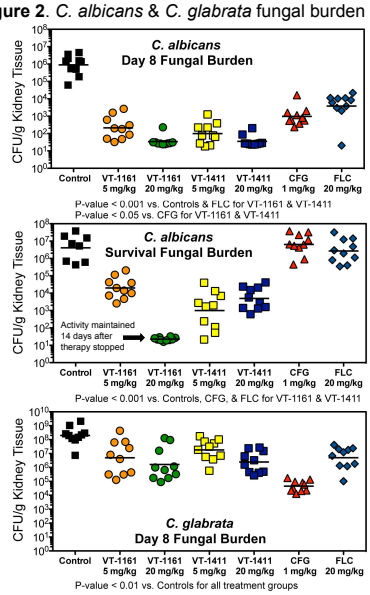
RESULTS

Figure 1. *C. albicans* survival results



P-value < 0.0001 for each dose of VT-1161, VT-1411, & CFG, and p = 0.025 for FLC vs. Controls (Median Survival)
P-value ≤ 0.0001 for each dose VT-1161 & VT-1411, p = 0.0031 for CFG, & p = 0.0867 for FLC vs. Control (% Survival)

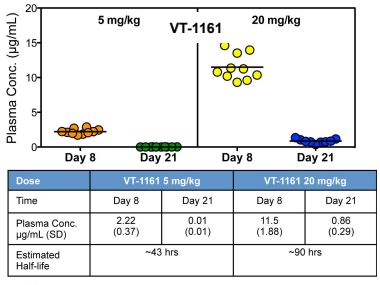
Figure 2. *C. albicans* & *C. glabrata* fungal burden results and drug concentration data.



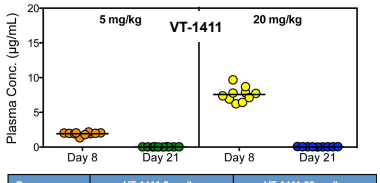
P-value < 0.001 vs. Controls & FLC for VT-1161 & VT-1411
P-value < 0.05 vs. CFG for VT-1161 & VT-1411

P-value < 0.001 vs. Controls, CFG, & FLC for VT-1161 & VT-1411

P-value < 0.01 vs. Controls for all treatment groups



Dose	VT-1161 5 mg/kg		VT-1161 20 mg/kg	
Time	Day 8	Day 21	Day 8	Day 21
Plasma Conc. µg/mL (SD)	2.22 (0.37)	0.01 (0.01)	11.5 (1.88)	0.86 (0.29)
Estimated Half-life	~43 hrs		~90 hrs	



Dose	VT-1411 5 mg/kg		VT-1411 20 mg/kg	
Time	Day 8	Day 21	Day 8	Day 21
Plasma Conc. µg/mL (SD)	1.92 (0.23)	0.03 (0.02)	7.58 (1.03)	0.05 (0.02)
Estimated Half-life	~58 hrs		~46 hrs	

CONCLUSIONS

VT-1161 & VT-1411 demonstrated potent in vivo efficacy against *C. albicans* and *C. glabrata*. Improvement in survival and reductions in fungal burden with these agents were significantly greater than those observed with fluconazole against *C. albicans*. These data demonstrate the potential utility of these agents against invasive candidiasis.

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