Efficacy of the Novel Fungal Cyp51 Inhibitor VT-1161 against Invasive Candidiasis Caused by Resistant *Candida albicans*

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BACKGROUND & OBJECTIVE

- *Candida* species are the fourth most common cause of nosocomial bloodstream infections in the U.S.
- *C. albicans* is the most common species associated with these infections.
- The clinical investigational agent VT-1161 is a fungal Cyp51-selective inhibitor with potent in vitro activity against *Candida* species including isolates that are resistant to fluconazole and caspofungin (Fothergill, ICAAC 2010, abstr. F-851 & ICAAC 2011, abstr. F-1381).
- VT-1161 has also demonstrated potent in vivo activity in an immunocompetent murine model of invasive candidiasis caused by azole and echinocandin susceptible *C. albicans.*
- Our objective was to evaluate the in vivo efficacy of this agent against invasive candidiasis caused by a fluconazole- and caspofungin-resistant *C. albicans* clinical isolate.

MATERIALS & METHODS

***Candida albicans* Isolate**

- *C. albicans* clinical isolate 43001 was used.
- The isolate was sub-cultured twice on SDA plates and grown in brain heart infusion broth overnight prior to in vivo studies.

Antifungal Susceptibility

- Minimum inhibitory concentrations (MIC) were measured by CLSI M27-A3 methodology.

Murine Model of Invasive Candidiasis

- Immunocompetent outbred male ICR mice were used.
- Mice were infected intravenously via the lateral tail vein. The target infecting inoculum was 1.5 x 10^6 cells/mouse.
- Antifungal therapy began 1 day post-inoculation and consisted of the following (N = 10 mice per group per arm):
  - Placebo (0.5% carboxymethylcellulose PO QD)
  - VT-1161 0.3 mg/kg PO QD
  - VT-1161 0.6 mg/kg PO QD
  - VT-1161 1.25 mg/kg PO QD
  - VT-1161 2.5 mg/kg PO QD
  - VT-1161 5 mg/kg PO QD
  - VT-1161 10 mg/kg PO QD
  - VT-1161 20 mg/kg PO QD
  - VT-1161 40 mg/kg PO QD
  - Fluconazole (FLC) 20 mg/kg PO BID
  - Caspofungin (CFG) 10 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. Plasma concentrations were measured by LC/MS-MS (OpAns, Durham, NC).

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RESULTS

Figure 1. Survival (A), and CFU/g on day 8 (B) and in the survival (C) arm.

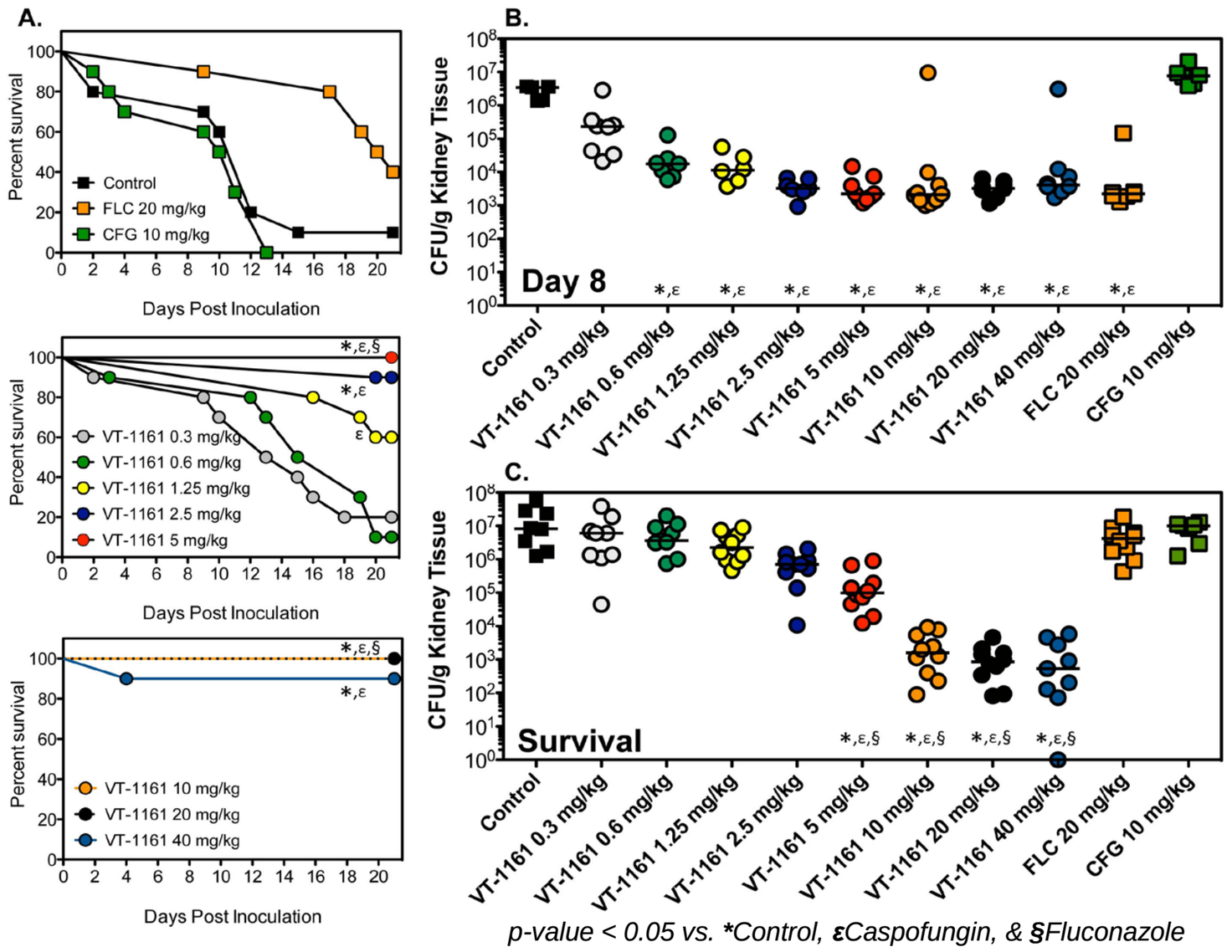
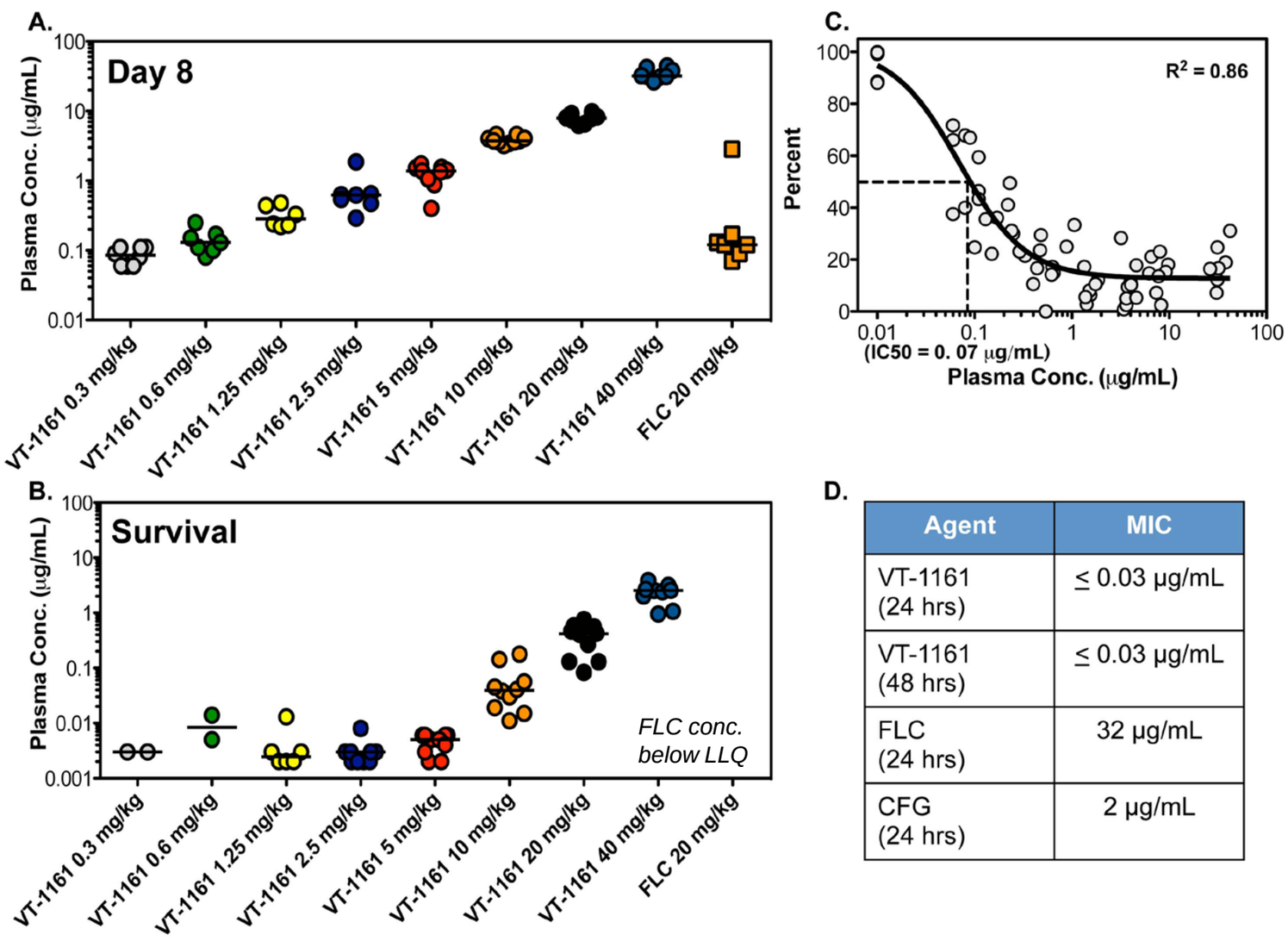


Figure 2. Plasma concentrations on day 8 (A), in the survival arm (B), day 8 concentration-response (CFU/g) curve (C), and minimum inhibitory concentrations (MIC; D).



CONCLUSIONS

A marked survival benefit was observed with VT-1161 against this resistant *C. albicans* isolate. VT-1161 at doses of ≥2.5 mg/kg/day significantly improved both median and percent survival compared to placebo and mice treated with high-dose caspofungin. Significant reductions in fungal burden on day 8 compared to placebo and caspofungin were also observed with VT-1161 at doses of ≥0.6 mg/kg/day with an in vivo trough IC50 value of 0.07 μg/mL. Fungal burden remained low at day 21 at doses of ≥5 mg/kg/day as plasma trough concentrations remained measurable and above the MIC 14 days after the last dose was administered.

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S ◆ A ◆ C ◆ M ◆ M
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