F-761

Prolonged Efficacy Following One Dose of a Novel Echinocandin, CD101, in a Neutropenic Mouse Model of Disseminated Candidiasis

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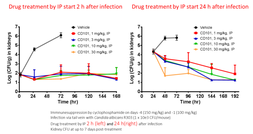
ABSTRACT

Background: CD101 is a novel echinocandin antifungal with long-acting pharmacokinetics and chemical stability that is being developed for once-weekly administration. The systemic candidiasis model with neutropenic mouse was employed to assess the duration of CD101 efficacy over a one week time course.

Methods: Neutropenic mice were infected by injection of *C. albicans* strain R303 suspensions into the tail vein, with an inoculum size of 10^3 CFU per mouse. Test agent and vehicle were administered to groups of 5 animals with a single intraperitoneal (IP) injection at 2 h or 24 h after infection. Animals were humanely euthanized at time points up to 7 days post-treatment then *Candida* counts were measured in kidney homogenates (CFU/g-tissue). Unpaired Student's *t* test was performed to determine the significance of treatment effects relative to the vehicle control groups.

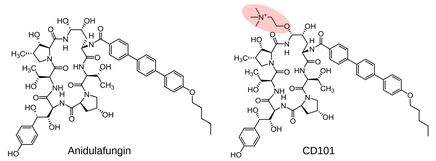
Results: CD101 was significantly efficacious when administered by the IP route across a wide range of doses and exposures that are projected to be achievable in the clinic (Panel A; $P \leq 0.005$ for the 24 and 72 h time points). Efficacy was observed when dosing was delayed to 24 h after infection (Panel B; $P < 0.005$ for the 48 h time point).



Conclusion: Efficacy of CD101 in the murine model indicates promise for the treatment of human systemic candidiasis with a once per week dosing regimen.

INTRODUCTION

Echinocandins are potent inhibitors of numerous pathogenic fungal species, including *Candida* spp. The primary pharmacodynamics (PD) of CD101, a novel echinocandin with improved pharmacokinetic (PK) properties relative to the other agents in the class, has been evaluated in both in vitro and in vivo studies with a focus on properties that support the proposed clinical use of once-weekly treatment of invasive/systemic candidiasis.



We aim to show that the superior pharmacokinetic properties of CD101 translates to prolonged efficacy in vivo in a neutropenic mouse model of disseminated candidiasis.

METHODS

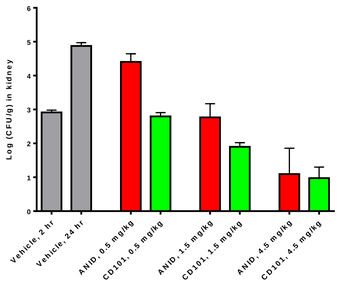
Minimum inhibitory concentration (MIC). The MIC in a broth susceptibility test was read at 50% inhibition of growth as defined by CLSI M27-A2. CD101 and anidulafungin (ANID) were each tested by 2-fold serial dilution from 16 to 0.0156 µg/mL. A 2 µL aliquot of each dilution was added to 198 µL of RPMI + MOPS with 1-5 x 10^3 CFU/mL of *C. albicans* (R303). The plates were incubated at 35-37°C for 48 hrs and then visually scored.

Mouse pharmacokinetics. PK of CD101 was evaluated in ICR mice (N=3/dose) after 1, 4, or 16 mg/kg intraperitoneal (IP) administration. Plasma was harvested at pre-selected times post-dose and analyzed by LC-MS/MS.

Neutropenic animal infection model. ICR mice (N=5/group) were rendered neutropenic by IP injections of cyclophosphamide at 150 mg/kg 4 days before infection (Day –4) and at 100 mg/kg 1 day before infection (Day –1). On Day 0, animals were inoculated with *C. albicans* (R303) intravenously (IV, 0.2 mL/mouse) with the inoculum size at 10^3 or 10^5 CFU depending on study. CD101 doses (at 1, 3, 10 or 30 mg/kg) were administered IP once at 2 or 24 h after infection. Animals were euthanized at time points up to 7 days post-treatment followed by CFU enumeration in kidney homogenates.

RESULTS

Figure 1. CD101 was efficacious at single doses of 0.5, 1.5, and 4.5 mg/kg given IP at 24 h after infection, demonstrating dose-dependent reductions of kidney burden that were greater than those of anidulafungin (ANID) at the 0.5 and 1.5 mg/kg doses and similar to that of ANID at the high dose.[1]



RESULTS (cont'd)

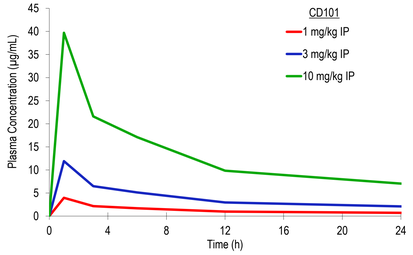
Table 1. Comparative MIC values of CD101 and ANID against *C. albicans* (R303) would not suggest that CD101 performs better than ANID in vivo.

Compound	MIC (µg/mL)
CD101	0.031
ANID	0.0078

Table 2. Comparative PK from IP administration of CD101 and ANID in ICR mouse showing superior pharmacokinetics of CD101 that likely accounts for better efficacy compared with ANID (given comparable protein binding of both compounds[2]).

Compound	Doses (mg/kg)	Dose-Normalized C_{max} ([µg/mL]/[mg/kg])	Dose-Normalized $AUC_{0\text{-}24}$ ([µg.h/mL]/[mg/kg])
CD101	1 - 16	3.5	33
ANID[3,4]	5 - 40	1.2	17

Figure 2. Mouse concentration-time profiles at different IP doses with terminal half-life >30 hrs; PK-PD analysis from dose fractionation studies of efficacy in a neutropenic mouse model is explored in a separate presentation.[5]



RESULTS (cont'd)

Figure 3. 7-day time-kill in neutropenic mouse *C. albicans* model suggests prolonged effect from as low as one dose of 1 mg/kg.

Drug treatment at 2 h post infection

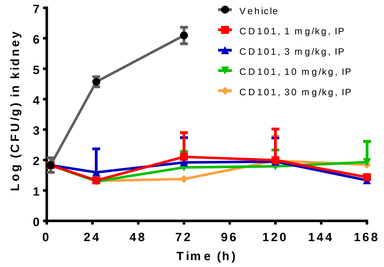
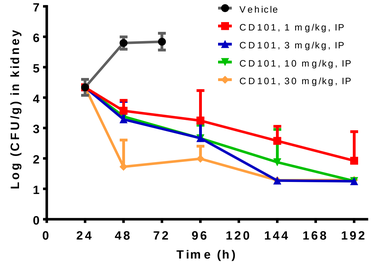


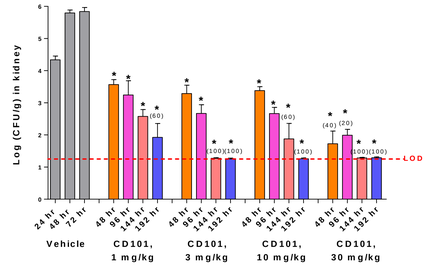
Figure 4. Even with a delayed treatment start at 24 hrs post-infection in the same neutropenic mouse *C. albicans* model, the efficacy was observed from as low as one dose of 1 mg/kg.

Drug treatment at 24 h post infection



RESULTS (cont'd)

Figure 5. Bar graph format of Figure 4. A >2-log reduction (*) in the kidney counts of the treatment groups compared to vehicle. The % of animals with counts below the LOD is in parentheses.



CONCLUSIONS

CD101 displays a concentration-dependent pattern of activity in vivo, consistent with that observed for other echinocandins.[6] Its superior PK properties suggest that a front-loaded CD101 dosing regimen is an optimal approach to maximize drug effect early in the course of therapy when the density of the pathogen is the greatest, providing the opportunity to increase the rate and extent of pathogen killing and resistance prevention.

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ACKNOWLEDGEMENTS

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