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Prophylactic, Single-Dose, Subcutaneous (SC) Administration of CD101 Shows Robust Efficacy in Neutropenic Mouse Models of Candidiasis and Aspergillosis

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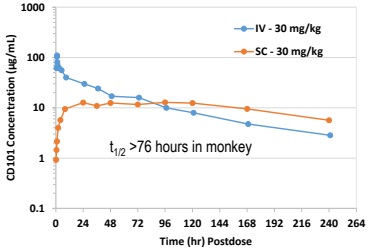
INTRODUCTION / PURPOSE

Fungal infections pose a significant public health burden with high morbidity and mortality. Immunocompromised patients continue to be at risk for opportunistic infections caused by fungal pathogens, such as *Candida* spp. and *Aspergillus* spp. CD101 is a novel echinocandin that has demonstrated robust preclinical efficacy and is differentiated from currently available echinocandins by a long-acting pharmacokinetic profile, allowing for once-weekly intravenous dosing, and exceptional stability and solubility, enabling formulating for subcutaneous (SC) administration.

Pharmacokinetic profile from a 30-mg/kg subcutaneuous (SC) administration in cynomolgus monkey indicates sustained exposures over >1 week[1].

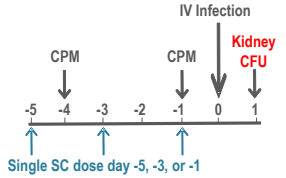


The potential for intermittent SC administration may extend the utility of CD101 beyond that of other echinocandins, to include antifungal treatment and prophylaxis in the outpatient setting. Neutropenic mouse models of candidiasis and aspergillosis were used to evaluate the in vivo efficacy of single SC doses of CD101 for prevention of fungal infections.

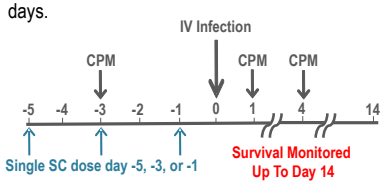
METHODS

Pharmacokinetics: CD101 was evaluated in ICR mice (N=3/dose) after a 10-mg/kg IV or SC dose. Plasma was harvested at selected times post-dose and analyzed by LC-MS/MS.

Candidiasis model: ICR mice (5/grp) were rendered neutropenic by cyclophosphamide (CPM) on day -4 (150 mg/kg) and day -1 (100 mg/kg), then challenged (day 0) with *Candida albicans* ATCC SC5314 via IV (100 µL, 10^5 CFU/mouse). Prior to challenge, mice were given one SC dose (5, 10, or 20 mg/kg) of CD101 on day -5, -3, or -1. At 24 hours postchallenge, kidneys were removed for CFU enumeration.

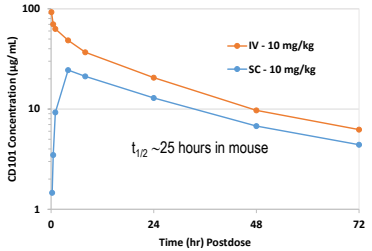


Aspergillosis model: ICR mice (6/grp) were rendered neutropenic by cyclophosphamide on days -3 (6 mg/mouse), +1 and +4 (2 mg/mouse). Challenge with *Aspergillus fumigatus* ATCC 13073 via IV (100 µL, 10^4 CFU/mouse) occurred on day 0. Prior to challenge, mice were given one SC dose (5, 10 or 20 mg/kg) of CD101 on day -5, -3, or -1. Survival was monitored for 14 days.

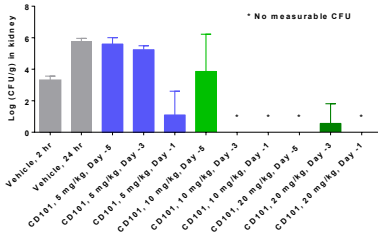


RESULTS

The PK profile of CD101 in mice following a 10-mg/kg SC dose shows a half-life of ~25 hrs with an absolute bioavailability of ~50%. It should be noted that the AUC from SC 10 mg/kg in mouse approximates an IV 200 mg dose in human.

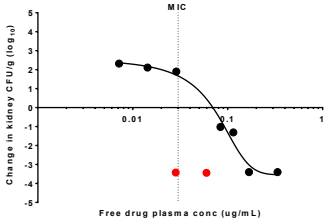


In the candidiasis (MIC=0.03 µg/mL) model, kidney CFU decreased with increasing doses of CD101 and prophylaxis occurring closer to challenge. Complete clearance was observed in all animals receiving 10 mg/kg at days -3 and -1 and all but one animal receiving 20 mg/kg on day -3. At doses of 5 or 10 mg/kg, prophylaxis with CD101 demonstrated a significant decrease in CFU at day -3 and -1. At the highest dose of 20 mg/kg, CD101 reduced CFU burden regardless of prophylactic treatment day.



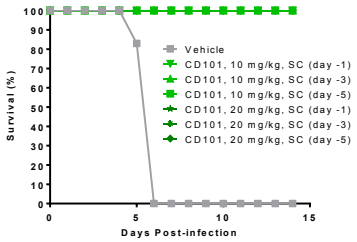
RESULTS (cont'd)

In general, a correlation was noted between free drug plasma concentration at time of infection over MIC (0.03 µg/mL) with higher free drug plasma concentration generating greater CFU reduction as shown in the graph below for the candidiasis model.



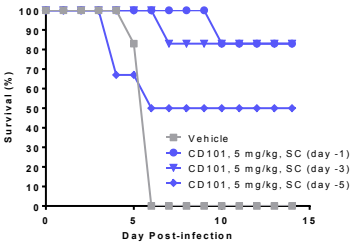
Exceptions were noted: Red symbols correspond to 10 and 20 mg/kg (Day -3 and -5 respectively) and indicate an apparent hysteresis where effective prophylaxis occurs despite low plasma conc, likely due to slower clearance from tissues.

In the aspergillosis (MEC=0.0078 µg/mL) model, survival was monitored for 14 days after challenge. All animals in the 10 and 20 mg/kg groups survived regardless of prophylactic treatment day.



RESULTS (cont'd)

The 5 mg/kg group showed increased survival when prophylaxis was given closer to challenge.



DISCUSSION / CONCLUSIONS

CD101, a novel echinocandin, administered to mice as a single SC dose of ≥10 mg/kg (equivalent to ≥200 mg IV human dose) was found to be protective against fungal infection in mice. Tissue residence times may play a vital role in CD101 prophylaxis efficacy, as has been shown for caspofungin[2] and micafungin[3] in similar studies. Though it remains to be studied, it is reasonable to anticipate that the protective effect may extend for a longer duration than in mouse as the $t_{1/2}$ of CD101 in human is >3x longer than in mouse.

CD101 may be a potential new agent for intermittent outpatient echinocandin treatment and prophylaxis of *Aspergillus* and *Candida*.

REFERENCES

1. Ong et al. ICHS-Infocus 2016
2. Louie et al., Antimicrob. Agents Chemother., 2005,49:5058–68
3. Lepak et al., Antimicrob. Agents Chemother., 2016,60:674–7

DISCLOSURES

V.O., K.B.: employees of Cidara Therapeutics, Inc.
S.R.L., L.M.: None.