Subcutaneous (SC) Injection of CD101, a Novel Echinocandin: Efficacious, Well-Tolerated and Sustained Drug Exposures

Voon Ong, Ph.D.
Cidara Therapeutics, Inc.
6310 Nancy Ridge Dr., Suite 101
San Diego, CA 92121 USA
vong@cidara.com

V. Ong[1], T. Sandison[1], G. Hough[1], M. Schlosser[1], K. Bartizal[1], M. Peek[2], S.R. Lopez[2]
[1]Cidara Therapeutics, San Diego, CA; [2]TransPharm Preclinical Solutions, Jackson, MI

INTRODUCTION

CD101 is a novel echinocandin displaying exceptional stability, solubility, long-acting pharmacokinetics (PK) and robust antifungal efficacy in animal models,[1,2] and is being developed for once-weekly intravenous (IV) administration for invasive fungal infections. CD101 was shown to have potent in vitro activity against reference strains of numerous *Candida* spp., *Aspergillus* spp., and other fungi with activity comparable to or superior to that of other echinocandins.[3] Capitalizing on the stability and solubility of CD101, we postulate that the availability of an intermittent subcutaneous (SC) administration may further extend the utility of CD101 as an antifungal beyond that of other currently marketed echinocandins. Preclinical studies were conducted to evaluate the efficacy, safety and PK of CD101 by SC administration.

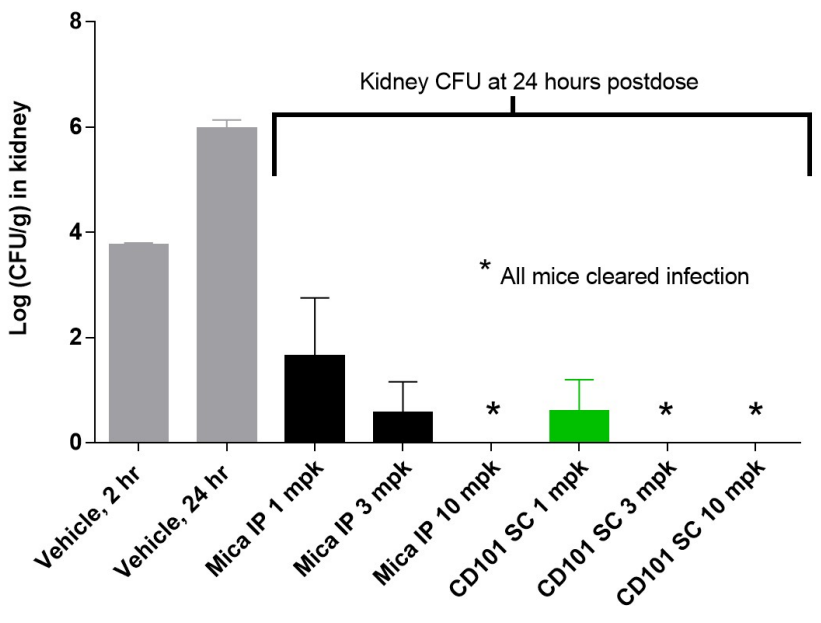
METHODS

Mouse Disseminated Infection Models. The efficacy of CD101 SC was studied in immunocompetent DBA/2 and neutropenic ICR mouse models of disseminated candidiasis. DBA/2 mice (5/grp) were challenged with *Candida albicans* SC5314 (ATCC: MYA-2876, fluconazole-sensitive human clinical isolate shown to be pathogenic in mice) via IV injection (100 µL, 5 log CFU/mouse) and treated with CD101 SC (1, 3 or 10 mg/kg). Micafungin via IP administration was tested as a positive control at the same 3 doses. At 24 hours following challenge, kidneys were harvested and processed for CFU enumeration. CD101 SC (5 mg/kg) was also tested in the same disseminated Candidiasis model using neutropenic ICR mice (cyclophosphamide days -4 [150 mg/kg] and -1 [100 mg/kg]) .

Monkey SC Tolerability/PK Study. One male and one female monkey were observed for up to 10 days following a single 30 mg/kg SC dose. In the same study, to determine the pharmacokinetics of CD101 following SC administration, whole blood samples were collected and the plasma was harvested at approximately 0.25, 0.5, 1, 2, 4, 8, 24, 36, and 48 hours, and 3, 4, 5, 7, and 10 days postdose. Plasma concentrations were then quantified by liquid chromatography with tandem mass spectrometric detection (LC-MS/MS).

RESULTS

In the DBA/2 mouse model, vehicle-treated mice showed mean log CFU of 3.8 at 2 hr increase to 6.1 at 24 hr. CD101 SC (1, 3, and 10 mg/kg) showed significant reduction in kidney CFU when compared to the vehicle control with complete CFU clearance at 3 or 10 mg/kg, and 4/5 animals in the 1 mg/kg group were completely cleared of CFU burden. A significant CFU reduction (4/5 animals showed complete clearance) was also observed in neutropenic ICR mice given a single SC dose of 5 mg/kg CD101.



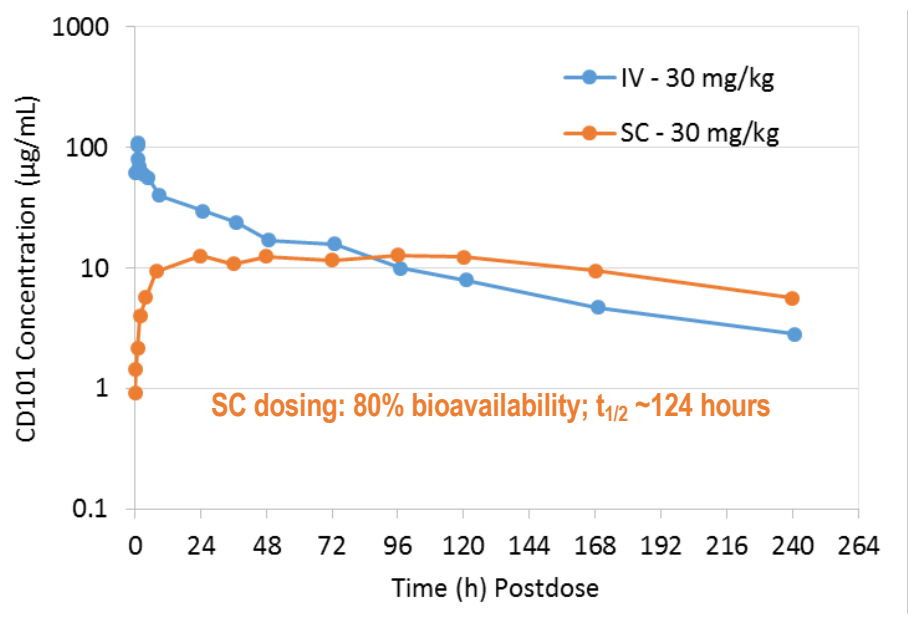
RESULTS (cont'd)

Previous toxicology studies by the IV route of administration conducted in cynomolgus monkeys have shown CD101 to be safe and well-tolerated at up to at least 30 mg/kg. During IND-enabling IV toxicology studies, no CD101-induced systemic adverse microscopic tissue injury were observed in either rats or monkeys, particularly for target organs previously shown to be important for human risk assessment with echinocandins[1] (e.g., liver).

Study Type	CD101 Summary Findings
Rat IV 4-week	NOAEL after repeat-dose was 34x efficacious exposure
Monkey IV 4-week	NOAEL after repeat-dose was 47x efficacious exposure
Genetic toxicology	No evidence of mutagenicity or clastogenicity
Rat/monkey IV safety pharmacology	No CNS, respiratory/cardiovascular concern
Monkey SC tolerability	No sign of irritation or local (injection site) adverse toxicity

Early PK studies in rats and monkeys had indicated that CD101 by SC dosing was well tolerated, although these initial studies were aimed at characterizing PK at lower doses (≤ 5 mg/kg). A separate toxicity study was designed to evaluate the tolerability of a SC dose of CD101 as a highly concentrated solution (100 mg/mL; 30 mg/kg) in the monkey. No sign of irritation or local (injection site) adverse toxicity was noted following a single high dose of 30 mg/kg CD101. There was also no effect on bodyweight or food consumption upon further follow-up observations for 10 days after administration.

The PK profile following SC administration of CD101 at 30 mg/kg showed that total exposure was comparable to IV (Figure). Maximum plasma concentration from SC administration was reached at ~24 hours and was sustained throughout the first week post-dose with decreasing concentrations beginning one week after injection.



CONCLUSIONS

CD101 as a single SC dose was efficacious, well tolerated and achieved sustained exposures with total AUC comparable to that of IV. CD101 SC could serve as a potential new agent and route of administration for intermittent outpatient echinocandin treatment and prophylaxis.

REFERENCES

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