Efficacy of CD101, a Novel Echinocandin, in the Treatment of Dermatophytosis Using a Guinea Pig (GP) Model

C. Hager[1], L. Long[1], M. A. Ghannoum[1]

[1]Center for Medical Mycology, Case Western Reserve University and University Hospitals Cleveland Medical Center, Cleveland, OH., 44106, USA

11100 Euclid Avenue,
Cleveland, OH 44106-5028
Phone: (216) 844-8580
FAX: (216) 844-1076
E-mail: mag3@po.cwru.edu

Introduction

Dermatophytosis, including onychomycosis, causes significant discomfort and affects patient quality-of-life, bringing about the need for more effective therapies. Echinocandin antifungals have been used clinically for over 15 years but not for treatment of dermatophytosis, as current echinocandins are limited to IV administration. CD101 is a novel echinocandin with stability that enables non-IV formulation. The aim of this study was to evaluate subcutaneous (SQ) administration of CD101 in the treatment of *Trichophyton mentagrophytes* dermatophytosis in a guinea pig (GP) model.

Materials and Methods

The experiments were performed following Institutional Animal Care and Use Committee guidelines. Male albino GPs with a body weight of 450 - 500g were housed in the Animal Resource Center assigned to rooms under standard conditions.

Inoculum:

- *T. mentagrophytes* (ATCC 24953) was sub-cultured on Potato Dextrose Agar (PDA) plates and incubated at 35°C for 5 - 7 days.
- The colonies were scraped from the plates using sterile phosphate buffered saline (PBS).
- Cells were washed in sterile PBS and harvested by centrifugation.

Inoculation:

- Each animal was anesthetized with a cocktail of ketamine and xylazine, intramuscularly.
- Hair was clipped and shaved on the back and a square of 2.5 cm × 2.5 cm was marked.
- The area was abraded with sterile fine grit sandpaper and inoculated with 10^7 conidia in 100µl.

Treatment Groups:

- Infected GPs were randomized into the following groups (5 per group): CD101 10 mg/kg, 20 mg/kg, or 40 mg/kg by SQ injection, terbinafine 10 mg/kg per os (PO) as a positive control, and a vehicle control by SQ injection.

Treatment Schedule:

- Beginning two hours post-inoculation, treatments were given on days 1 & 8 of the study.

Materials and Methods (cont.)

Mycological Evaluation:

- On day 12 post-inoculation, ten hair samples from each quadrant were inoculated onto PDA plates and incubated at 35ºC for 2 days.
- The fungal growth at the hair root was examined under a stereomicroscope.
- The effectiveness of a compound was expressed as percentage relative to the vehicle control group.

Clinical Evaluation:

- Local changes to the area were clinically assessed and scored on day 12.
- The assessment of clinical efficacy for each treatment group is expressed as percentage relative to the vehicle control group.

Percent Efficacy:

- **%** efficacy = 100 – (T x 100/ K)
- Where T = score in test group, and K = score in untreated control.

Statistical analysis:

Statistical significance of clinical and mycological study data was determined using a one-way analysis of variance (ANOVA) with a Bonferroni post hoc test. The treated groups were compared to the untreated control and to one another to determine antifungal activity.

Results

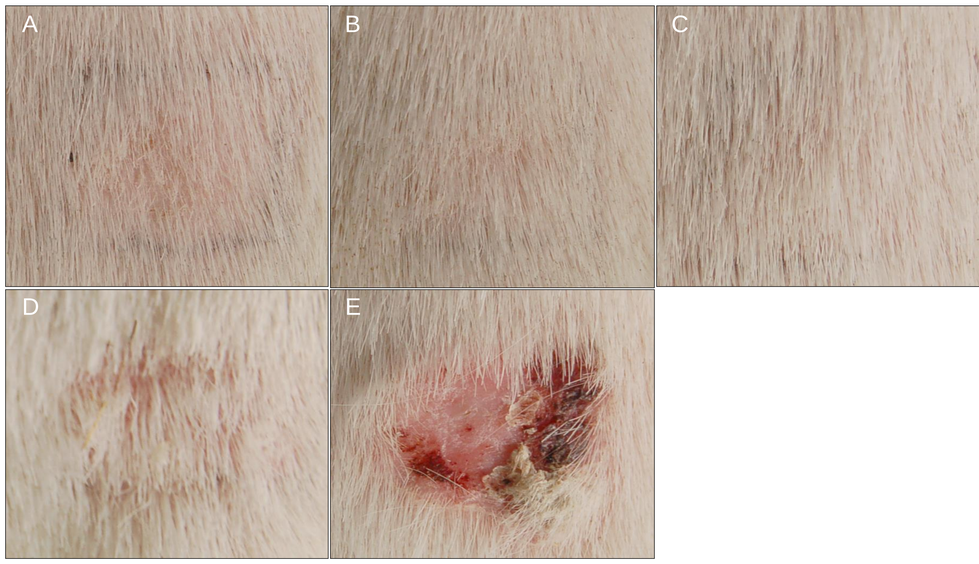
Clinical efficacy:

- Table 1 and Figure 1 show the clinical efficacy of each treatment.
- As expected, the vehicle control GPs showed hair loss and ulcerated, scaly skin.
- Percent efficacies for groups treated with CD101 10, 20, and 40 mg/kg on days 1 & 8 were 90.5, 94.2, and 98.4%, respectively, and 76.8% for terbinafine 10 mg/kg on days 1 & 8.
- All treatment groups showed significant efficacy compared to the vehicle control (P<0.001).
- The CD101 treated groups showed significant efficacy compared to the terbinafine treated group (P<0.001).

Mycological efficacy:

- The vehicle control group behaved as expected having the highest average fungal positive hairs.
- Percent efficacies for groups treated with CD101 10, 20, and 40 mg/kg on days 1 & 8 were 80.9, 82.9, and 98.5%, respectively, and 54.2% for terbinafine 10 mg/kg on days 1 & 8.
- All treatment groups showed significant efficacy compared to the vehicle control (P<0.001).
- The CD101 treated groups showed significant efficacy compared to the terbinafine treated group (P<0.001).

Figure 1. Clinical Appearance on day 12.



A. CD101 10 mg/kg days 1 & 8 **B.** CD101 20 mg/kg days 1 & 8 **C.** CD101 40 mg/kg days 1 & 8 **D.** Terbinafine 10 mg/kg days 1 & 8 **E.** Vehicle control

Table 1. Percent Efficacy

Test Compounds	Dose (mg/kg)	Route of Administration	Percent Efficacy	
			Mycological	Clinical
CD101	10	SC	80.9*	90.5*
CD101	20	SC	82.9*	94.2*
CD101	40	SC	98.5*	98.4*
Terbinafine	10	PO	54.2*	76.8*
Vehicle	NA	SC	NA	NA

* P-value of < 0.001, when compared to the vehicle control.

Conclusions

All CD101 treated groups showed significant clinical and mycological efficacy compared to the vehicle treated control and terbinafine treated groups. Our findings demonstrate that CD101 dosed once weekly possesses potent mycological and clinical efficacy in a GP model of dermatophytosis. Further evaluation is warranted.

References

1.Ghannoum MA, Hossain MA, Long LA, Mohamed S, Reyes G, and Mukherjee PK. Evaluation of Antifungal Efficacy in an Optimized Animal Model of *Trichophyton mentagrophytes*-Dermatophytosis. *J Chemother.* 16(2): 139-144 (2004).

Acknowledgements

This study was supported by Cidara Therapeutics, Inc.