ABSTRACT
Introduction: All commercially available echinocandins are fungicidal agents administered once daily, with efficacy shown for AUC0-24:F > 200 against Candida albicans. CD101 is a novel echinocandin with a concentration-dependent pattern of fungicidal activity in vitro and in long-term murine infections, (10,000 fold more potent).
Research Question or Hypothesis: Given these distinct characteristics, it is likely that the shape of the time-concentration profile may have clinical significance.
Study Design: Preclinical pharmacokinetic and dose fractionation studies.
Methods: The same total AUC was administered to groups of neutropenic ICR mice infected with Candida albicans (10^7 CFU) using 3 different schedules. A total CD101 dose of 2 mg/kg was delivered daily (0.29 mg/kg/day), twice weekly (1 mg/kg x 2) or once daily (2 mg/kg). Animals were rendered neutropenic by IP injection of 2 g/kg Mafenide and 2 g/kg Myelomune to achieve a neutrophil count of ~1000. Groups of 5 animals were treated over 14 days.
Results: As shown in Figure 1, fungicidal activity was observed at 168 hours following administration of single CD101 doses (2 mg/kg). However, the magnitude of net change in log CFU from baseline at 168 hours was similar regardless of regimen. The results of the dose fractionation study are displayed in Figure 2. The magnitude of net change in log CFU from baseline at 168 hours was similar regardless of fractionation schedule (Figure 2). However, results within the CD101 2 mg/kg group varied by the fractionation schedule.
Conclusions: This theory was tested using data from an animal model in which the same total weekly dose was administered as a single IV dose or in equal divided doses of either 1 mg/kg twice weekly or 2 mg/kg once daily. Paired kidneys were infected with 3 different schedules. A total CD101 dose of 2 mg/kg was delivered daily (0.29 mg/kg/day), twice weekly (1 mg/kg x 2) or once daily (2 mg/kg). Animals were rendered neutropenic by IP injection of 2 g/kg Mafenide and 2 g/kg Myelomune to achieve a neutrophil count of ~1000. Groups of 5 animals were treated over 14 days.
RESULTS
Pharmacokinetic Study
- CD101 exhibited linear PK over the dose-ranged studied (1 to 14 mg/kg PF).
- A bio-constant model best described the PK data. Model PF was deployed in Figure 1.
- Observed (blue solid circles) and model fitted (lines) CD101 concentrations versus time following administration of single dose CD101 regimens.

Dose-Fractionation Study
- The results of the dose fractionation study are displayed in Figure 2.
- The magnitude of net change in log CFU from baseline at 168 hours was similar regardless of fractionation schedule within the CD101 2 mg/kg and 7 mg/kg dosing groups.
- However, results within the CD101 2 mg/kg group varied by the fractionation schedule.

Table 1. Summary of CD101 dosing regimens evaluated

<table>
<thead>
<tr>
<th>Total Dose</th>
<th>Fractionation Schedule</th>
<th>CFU from baseline at 168h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7 mg/kg</td>
<td>Single Dose</td>
<td>1.7 mg/kg</td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>Single Dose</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>7 mg/kg</td>
<td>Single Dose</td>
<td>7 mg/kg</td>
</tr>
</tbody>
</table>

CONCLUSIONS
Three CD101 regimens with similar total exposure, yet different exposure shapes, displayed considerably different magnitude of net change in log CFU from baseline at 168 hours. This supports the hypothesis that the shape of the time-concentration profile may have clinical significance.

ACKNOWLEDGMENTS
This work was supported in part by Cidara Therapeutics, Inc. Financial support for this project was provided by Cidara Therapeutics, Inc.

REFERENCES

Exposure Shape Matters
- The change in log CFU, CHI reduction from baseline at 168 hours for fractionation of the CD101 2 mg/kg group is displayed in Figure 3.
- When a total dose of 2 mg/kg was delivered daily (0.29 mg/kg/day), the magnitude of net change in log CFU from baseline at 168 hours was similar to the no treatment control group.
- However, when 2 mg/kg was delivered as a single dose, there was a >2-log CHI reduction from baseline at 168 hours.
- The 2 mg/kg x 2 and 0.29 mg/kg x 7 regimen showed similar cumulative CD101 exposures, but dosing was different, as shown in Figure 2. Despite having similar exposures, which influences efficacy.

Pharmacolocial Basis of CD101 Efficacy: Exposure Shape Matters
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Figure 3. Mean (bar) and range (error bars) change in log CHI from baseline allowing administration of CD101 2 mg/kg given fractionation schedule.

Figure 4. Three CD101 regimens with similar total exposure, yet different exposure shapes, displayed considerably different magnitude of net change in log CHI from baseline at 168 hours. This supports the hypothesis that the shape of the time-concentration profile may have clinical significance.

Figure 5. A bio-constant model best described the PK data. Model PF was deployed in Figure 1.