Efficacy of a Novel Echinocandin, CD101, in a Mouse Model of Azole-Resistant Disseminated Candidiasis

L. Miesel¹, K-Y Lin¹, J. C. Chien¹, M. L. Hsieh¹, V. Ong², and K. Bartizal²

¹Eurofins Panlabs, Taipei, Taiwan
²Cidara Therapeutics Inc., San Diego, CA

LynnMiesel@eurofins.com
Disclosures

- Lynn Miesel is a Eurofins Pharma Discovery Services employee.
- This research was performed under contract between Eurofins Panlabs Taiwan and Cidara Therapeutics.
Rationale

- Candidiasis is becoming more prevalent among nosocomial infections, ranking fourth among BSIs in the USA (1)
- *C. albicans* is the predominant cause but non-*albicans* species are increasingly prevalent
- Resistance to azole antifungals is now more common due to widespread fluconazole use
- The IDSA and ESCMID now recommend echinocandins as first-line treatment (2, 3)
- This study aimed to test CD101 for potential use against azole-resistant candidiasis using a disseminated mouse infection model

(2) PG Pappas et al. 2015 Clinical Infectious Disease
(3) OA Cornely et al. 2012 Clin Microbiol Infect. 18 Suppl 7 p19–37
## CD101, a highly stable echinocandin

- **Enhanced chemical stability**
- **Long-acting pharmacokinetics**
- **In development for once-weekly therapy**

<table>
<thead>
<tr>
<th>Species</th>
<th>Caspofungin&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Anidulafungin&lt;sup&gt;b&lt;/sup&gt;</th>
<th>CD101&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD Rat</td>
<td>6-7</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>Dog</td>
<td>N/A</td>
<td>12</td>
<td>53</td>
</tr>
<tr>
<td>Cyno Monkey</td>
<td>N/A</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Chimpanzee</td>
<td>5-8</td>
<td>30</td>
<td>81</td>
</tr>
</tbody>
</table>

**In vitro potency of CD101 against C. albicans**

**Candida albicans**  
2012 – 2014 clinical isolates ($n=100$)*

<table>
<thead>
<tr>
<th></th>
<th>Azole-susceptible ($n=90$)</th>
<th>Fluconazole-resistant ($n=10$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC$_{90}$ (µg/mL)</td>
<td>0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>

- CD101 has potent in vitro activity against azole-susceptible and -resistant clinical isolates

Azole-resistant *C. albicans* R357

*C. albicans* strain R357 is an azole-resistant human blood isolate

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Endpoint (% inhibition)</th>
<th>MIC (µg/mL)</th>
<th>Susceptibility (CLSI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>50%</td>
<td>&gt;64</td>
<td>R</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>50%</td>
<td>&gt;64</td>
<td>R</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>50%</td>
<td>&gt;64</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>100%</td>
<td>0.5</td>
<td>S</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>50%</td>
<td>0.25</td>
<td>S</td>
</tr>
<tr>
<td>CD101</td>
<td>50%</td>
<td>0.125</td>
<td></td>
</tr>
</tbody>
</table>

Azole resistance in R357
- CaERG11 increased expression: 12.3x
- CaERG11 changes: D116E, D153E, and E266D
- No significant changes in CDR1 or MDR1 expression
Azole-resistant *C. albicans* R357 disseminated infection model

**Procedure**

- **Host:** ICR Mouse
- **Neutropenia** – cyclophosphamide (cpm) days -4, -1
- **Infection,** *Candida albicans* R357, $10^5$ CFU/mouse
- **Test article administration:** one (qd) dose
  - 2 hr after infection
  - **Vehicle,** CD101 – Intraperitoneal (IP)
  - **Amphotericin B** (AM-B) – Intravenous (IV)
  - **Fluconazole** (FLU) – oral (PO)
- **Kidney counts (CFU /g)** – 48, 72 hr after infection
Azole-resistant *C. albicans* R357 disseminated infection model

Model development – vary the inoculum density

Inoculum count (CFU); Infection duration (hr)
Azole-resistant *C. albicans* R357 disseminated infection model

Initial 2 hr counts, Vehicle, IV, 72 hr, FLU, 20 mg/kg, PO, 72 hr, AM-B, 1 mg/kg, IV, 72 hr, AM-B, 3 mg/kg, IV, 72 hr

Efficacy of antifungals

Log$_{10}$ CFU/g kidney

* * #
Azole-resistant *C. albicans* R357 disseminated infection model

**Efficacy of antifungals - fungal counts**

**48 hr**

- **Initial 2 hr counts**
  - Vehicle, IP, 48 hr
  - FLU, 20 mg/kg, PO
  - AM-B, 1 mg/kg, IV
  - AM-B, 3 mg/kg, IV
  - CD101, 3 mg/kg, IP
  - CD101, 10 mg/kg, IP
  - CD101, 30 mg/kg, IP

**72 hr**

- **Initial 2 hr counts**
  - Vehicle, IP, 72 hr
  - FLU, 20 mg/kg, PO
  - AM-B, 1 mg/kg, IV
  - AM-B, 3 mg/kg, IV
  - CD101, 3 mg/kg, IP
  - CD101, 10 mg/kg, IP
  - CD101, 30 mg/kg, IP

<table>
<thead>
<tr>
<th>Log$_{10}$ CFU/g kidney</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle, IP, 48 hr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>#</td>
<td>#</td>
<td>*</td>
<td>#</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td>FLU, 20 mg/kg, PO</td>
<td>*</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td>AM-B, 1 mg/kg, IV</td>
<td></td>
<td></td>
<td></td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td>AM-B, 3 mg/kg, IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>#</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td>CD101, 3 mg/kg, IP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD101, 10 mg/kg, IP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD101, 30 mg/kg, IP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ≥99% reduction
# $p < 0.05$ vs. vehicle
Azole-resistant *C. albicans* R357 disseminated infection model

**Efficacy of antifungals - difference in counts**

- **48 hr**
  - Initial 2 hr counts
    - Vehicle, IP, 48 hr
    - FLU, 20 mg/kg, PO
    - AM-B, 1 mg/kg, IV
    - CD101, 3 mg/kg, IV
    - CD101, 10 mg/kg, IP
    - CD101, 30 mg/kg, IP

- **72 hr**
  - Initial 2 hr counts
    - Vehicle, IP, 72 hr
    - FLU, 20 mg/kg, PO
    - AM-B, 1 mg/kg, IV
    - CD101, 3 mg/kg, IV
    - CD101, 10 mg/kg, IP
    - CD101, 30 mg/kg, IP
CD101, a novel echinocandin, demonstrated efficacy in a disseminated infection model of azole-resistant candidiasis.

Efficacy persisted 72 hr consistent with long-acting pharmacokinetics.

CD101 treatment resulted in a fungicidal effect.