Echinocandin PK-PD

• Echinocandins have only been in use for 10 years, caspofungin being the first approved agent in 2001

• In vitro and in vivo, echinocandins display a concentration-dependent pattern of activity against Candida spp¹
  - That is, as drug concentration increases, so too does the extent and rate of microbial killing

• The PK-PD index that best describes antifungal activity varies among echinocandins

CD101, a Novel Echinocandin

- Developed by Cidara Therapeutics, CD101 is a structural analog of anidulafungin
  - Long acting echinocandin
  - Reduced hepatotoxicity
  - Intravenous and topical formulations
- Currently entering Phase 1 clinical development for candidemia and invasive candidiasis
There were two objectives of these studies:

- To determine the pharmacodynamics driver most closely associated with CD101 efficacy
- To determine the magnitude of the PK-PD measure associated with net fungal stasis and a 1- and 2-$\log_{10}$ CFU reduction from baseline
**Pharmacokinetics Studies**

- Plasma PK data were obtained from neutropenic mice administered a single dose of CD101.
- 5 mice per time point per dose.
- Plasma samples were assayed for CD101 using LC/MS/MS with a lower limit of quantification of 0.02 μg/mL.

<table>
<thead>
<tr>
<th>Study</th>
<th>Route of Administration</th>
<th>Doses (mg/kg)</th>
<th>Sampling Times (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB26207</td>
<td>Intravenous</td>
<td>0.4</td>
<td>3, 6, 12, 24, 36, 48</td>
</tr>
<tr>
<td>“Other”</td>
<td>Intravenous</td>
<td>1</td>
<td>0.083, 0.5, 1, 4, 8, 24, 48, 72</td>
</tr>
<tr>
<td>AB29611</td>
<td>Intraperitoneal</td>
<td>1, 4, 16</td>
<td>0, 1, 3, 6, 12, 24, 48, 72, 96</td>
</tr>
</tbody>
</table>
Dose-Fractionation Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Route of Administration</th>
<th>Treatment Start&lt;sup&gt;a&lt;/sup&gt; (h)</th>
<th>Daily Doses (mg/kg)</th>
<th>Dosing Intervals (h)</th>
<th>Observation Time&lt;sup&gt;b&lt;/sup&gt; (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB26207</td>
<td>Intravenous</td>
<td>2</td>
<td>0.4, 0.8</td>
<td>6, 8, 12, 24</td>
<td>3, 6, 12, 24, 36, 48</td>
</tr>
<tr>
<td>AB29211</td>
<td>Intraperitoneal</td>
<td>24</td>
<td>3, 30</td>
<td>6, 8, 12, 24</td>
<td>48, 96, 192</td>
</tr>
</tbody>
</table>

<sup>a</sup>Relative to inoculation

<sup>b</sup>Relative to treatment start

- Male ICR mice (5 per regimen and observation time) were rendered neutropenic by two IP cyclophosphamide injections

- Animals were inoculated with *Candida albicans* R303 (2.6 x 10<sup>3</sup> CFU/mouse) via tail vein

- Treatment duration was 48 hours in both studies

- Paired kidneys were harvested, homogenized, serially diluted, and plated for CFU determination
METHODS

PK and PK-PD Modeling

• Data from the PK studies were analyzed using S-ADAPT
  o Population models fit to the data
  o Exposures for PK-PD dosing regimens generated using post-hoc PK parameters

• Data from the efficacy studies were modeled using a Hill-type model and non-linear least squares regression
  o The relationship between \( \log_{10} \text{CFU at 24 h} \) and \( \text{AUC}_{0-24} : \text{MIC} \), \( \text{C}_{\text{max}} : \text{MIC} \) and \( \%T>\text{MIC} \) was evaluated
Mouse PK Differences Due to Route

RESULTS

Dose (mg/kg)
- 0.4
- 1
- 4
- 16

Study
- AB26207
- AB29611
- OTHERSTUDY

Dose-Normalized CD101 Conc. (ug/mL)

Time Since Dose (h)
RESULTS
Pharmacokinetics Studies

![Graphs showing the concentration of CD101 over time for different doses and routes of administration.]

- **1 mg/kg IP**
- **4 mg/kg IP**
- **16 mg/kg IP**
- **0.4 mg/kg IV**
- **1 mg/kg IV**
RESULTS

Comparison of PK-PD Data

![Graph showing comparison of PK-PD data for AB26207 and AB29611. The x-axis represents time post-inoculation (h), and the y-axis represents change in Log_{10} CFU. The graph includes data points for different treatment groups, such as CD101 and Vehicle, with various daily doses (0, 0.4, 0.8, 3, 30 mg/kg).]
RESULTS
PK-PD Correlations – IV Dosing

The data in these figures is from the 0.4 mg/kg arm of AB26207 only.
RESULTS

PK-PD Correlations – CD101 IP Dosing

$r^2 = 0.844$

$r^2 = 0.847$

$r^2 = 0.847$

Free-Drug AUC:MIC

Free-Drug $C_{\text{max}}$:MIC

Free-Drug %T>MIC

Change in $\log_{10}$ CFU

Legend:
- Red: Control
- Blue: Q6
- Green: Q8
- Orange: Q12
- Purple: Q24
## RESULTS

### PK-PD Correlations – CD101 IP Dosing

<table>
<thead>
<tr>
<th>Parameter&lt;sup&gt;a&lt;/sup&gt;</th>
<th>$f_{\text{AUC}:\text{MIC}}$</th>
<th>$f_{\text{Cmax}:\text{MIC}}$</th>
<th>%T&gt;MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV</td>
<td>IP</td>
<td>IV</td>
</tr>
<tr>
<td>$E_0$</td>
<td>2.29 (0.14)</td>
<td>1.58 (0.16)</td>
<td>2.29 (0.13)</td>
</tr>
<tr>
<td>Emax</td>
<td>4.40 (0.20)</td>
<td>2.77 (0.44)</td>
<td>4.39 (0.20)</td>
</tr>
<tr>
<td>Hill</td>
<td>31.8 (5.14)</td>
<td>1.00 (2.51)</td>
<td>18.1 (2.92)</td>
</tr>
<tr>
<td>EC$_{50}$</td>
<td>6.52 (0.04)</td>
<td>5.16 (15.6)</td>
<td>0.51 (0.00)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Magnitude&lt;sup&gt;b&lt;/sup&gt;</th>
<th>$f_{\text{AUC}:\text{MIC}}$</th>
<th>$f_{\text{Cmax}:\text{MIC}}$</th>
<th>%T&gt;MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Stasis</td>
<td><strong>6.53</strong></td>
<td><strong>6.84</strong></td>
<td><strong>0.51</strong></td>
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<tr>
<td>1-log$_{10}$ drop</td>
<td>6.73</td>
<td>70.1</td>
<td>0.54</td>
</tr>
<tr>
<td>2-log$_{10}$ drop</td>
<td>7.32</td>
<td>NA</td>
<td>0.62</td>
</tr>
</tbody>
</table>

<sup>a</sup>PK-PD parameters reported as mean (SE)

<sup>b</sup>Magnitude of the PK-PD index associated with the given effect
DISCUSSION

What have we learned?

- Dose-fractionation studies did not discriminate between the three PK-PD indices
  - This is likely due to CD101’s long half-life in mice ($t_{1/2} \sim 45-70$ h)
  - Repeat studies with lower doses may help to break the colinearity between $C_{\text{max}}:\text{MIC}$, $\text{AUC}_{0-24}:\text{MIC}$ and $\%T>\text{MIC}$
- Like other echinocandins, the $\text{AUC}_{0-24}:\text{MIC}$ ratio described the relationship between exposure and response well
- Despite the pronounced differences in the design of the IV and IP dose-fractionation studies, the magnitude of the PK-PD indices necessary to effect stasis in fungal growth were similar
- We recommend $\text{AUC}_{0-24}:\text{MIC}$ over $C_{\text{max}}:\text{MIC}$ and $\%T>\text{MIC}$ for dose optimization as AUC is more precisely estimated
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THANK YOU FOR YOUR ATTENTION