Prolonged Efficacy Following One Dose of a Novel Echinocandin, CD101, in a Neutropenic Mouse Model of Disseminated Candidiasis

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ABSTRACT

Background: CD101 is a novel echinocandin with long-acting pharmacokinetics and clinical activity. It is being advanced for once-weekly parenteral therapy. A rodent model comparing neutropenic mice treated with CD101 once weekly to a once-weekly dose of a marketed echinocandin was used to assess the duration of CD101 efficacy over a seven-week time course.

Methods: Neutropenic mice were infected with C. albicans strain R303 suspensions into the tail vein, with an inoculum size of 1 × 10^7 CFU per mouse. Treatment and vehicle were administered to groups of animals with a single intraperitoneal (IP) injection at 2 h before infection (Day 1). Drug treatment was followed by CFU enumeration in kidney homogenates. In a separate presentation, pharmacokinetic (PK) fractionation studies of efficacy in a neutropenic mouse model is explored in a separate presentation.

Results: CD101 was significantly efficacious when administered by the IP route across a range of doses and exposures that are projected to be achievable in the clinic (Panel A; P < 0.005 for the 48 and 96 hr time point). Mouse pharmacokinetics. PK of CD101 was evaluated in ICR mouse (N=3/group) after 1, 4, or 16 mg/kg intraperitoneal (IP) administration. Plasma was harvested at pre-selected time points and dose and analyzed by LC-MS/MS.

Neutrophic animal infection model. ICR-mice (N=5/group) were rendered neutrophilic by IP injections of cyclophosphamide at 150 mg/kg 4 days before infection (Day -4) and at 100 mg/kg 1 day before infection (Day -1). On Day 0, animals were inoculated with C. albicans (R303) intravenously (i.v., 0.2 ml/mouse) with the inoculum size at 10^3 or 10^5 CFU depending on study. CD101 doses (1, 3, 10 or 30 mg/kg) were administered IP at 2 or 24 h after infection. Animals were euthanized at time points up to 7 days post-treatment followed by CFU enumeration in kidney homogenizes.

Conclusions: Efficacy of CD101 in the neutropenic model indicates promise for the treatment of C. albicans (R303) would not suggest that CD101 performs better than ANID in vivo.

RESULTS (cont’d)

Table 1. Comparative MIC values of CD101 and ANID against C. albicans (R303) would not suggest that CD101 performs better than ANID in vivo.

<table>
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<tr>
<th>Compound</th>
<th>MIC (µg/mL)</th>
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<tr>
<td>CD101</td>
<td>0.031</td>
</tr>
<tr>
<td>ANID</td>
<td>0.0078</td>
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Figure 1. CD101 was efficacious at single doses of 0.5, 1.5, and 4.9 mg/kg given IP at 24 h after infection, demonstrating dose-dependent reductions of kidney burden that were greater than those of ANID (at the 0.5 and 1.5 mg/kg doses) and similar to that of ANID at the high dose.

Figure 2. Mouse concentration-time profiles at different IP doses with a peak half life (>30 hr). PK analysis from dose fractionation studies of efficacy in a neutropenic mouse model is explored in a separate presentation.

Figure 3. 7-day time-kill in neutrophic mouse C. albicans model suggests prolonged effect from as low as one dose of 1 mg/kg.

Figure 4. Even with a delayed treatment start at 24 hrs post-infection in the same neutropenic mouse C. albicans model, the efficacy was observed from as low as one dose of 1 mg/kg.

CONCLUSIONS

CD101 displays a concentration-dependent pattern of activity in vivo, consistent with that observed for other echinocandins. Its superior PK properties suggest that a front-loaded CD101 dosing regimen is an optimal approach to maximize drug effect early in the course of therapy when the density of the pathogen is the greatest, providing the opportunity to increase the rate and extent of pathogen killing and resistance prevention.

REFERENCES

1. ICAC 2015, Poster T-750.
2. ICAC 2015, Poster A-015.
5. ICAC 2015, Bida Session 044: Pharmacokinetics/Pharmacodynamics (PK/PD) of a Novel Echinocandin, CD101, in a Neutropenic Murine Disseminated Candidiasis Model.

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