Echinocandins are potent inhibitors of numerous pathogenic fungal species, including Candida spp. The primary pharmacodynamics (PD) of CD101, a novel echinocandin with improved pharmacokinetic (PK) properties relative to the other agents in the class, has been evaluated in both in vitro and in vivo studies with a focus on properties that support the proposed clinical use of once-weekly treatment of invasive systemic candidiasis.

Figure 1. CD101 was efficacious at single doses of 0.5, 1.5, and 4.5 mg/kg given IP at 24 h after infection, demonstrating dose-dependent reductions of kidney burden that were greater than those of anidulafungin (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 halflife > 30 h. PK analysis from dose fractionation studies of efficacy in a neutropenic mouse model is explored in a separate presentation.

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

Table 2. Comparative PK from IP administration of CD101 and ANID in ICR mice showing superior pharmacokinetics of CD101 that likely accounts for better efficacy compared with ANID (given comparable protein binding of both compounds).

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.

Figure 5. Bar graph format of Figure 4. A >2-log reduction (*) in the kidney cultures from the treatment group compared to vehicle. The % of animals with counts below the LOD is in parentheses.

Results (cont’d)

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. ICACI 2015, Poster F-750.
2. ICACI 2015, Poster A-015.
5. ICACI 2015, Bible Session 044: Pharmacokinetics/Pharmacodynamics (PK/PD) of a Novel Echinocandin, CD101, in a Neutropenic Mouse Disseminated Candidiasis Model.