O425
1-hour Oral Session
Challenges in antifungal treatment

The safety and single-dose pharmacokinetics of CD101IV: results from a phase 1, dose-escalation study

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Background: CD101 IV is a novel echinocandin being developed as a once-weekly administered antifungal for candidemia and invasive candidiasis. CD101 has demonstrated potent in vitro and in vivo activity against a broad range of *Candida* and *Aspergillus* species. CD101 IV was evaluated in a randomized, double-blind, placebo-controlled, dose-escalation study designed to establish the safety, tolerability, and pharmacokinetics of single intravenous (IV) doses of CD101 IV.

Material/methods: In four sequential cohorts of eight subjects (n=6, active; n=2, placebo), CD101 was administered IV as a single dose infused over 1 h (50 mg, 100 mg, 200 mg, 400 mg), with dose escalation determined by pre-defined safety criteria. Extensive plasma and urine sampling over 21 days was performed to assess the pharmacokinetics of CD101 IV. Safety and tolerability was assessed by adverse events (AEs), vital signs, physical exams, electrocardiograms (ECGs), haematology and clinical chemistry laboratories up to 21 days after dosing.

Results: A total of 32 subjects were randomized to the study, with 31 subjects completing all study assessments. One subject prematurely withdrew for personal reasons unrelated to safety or tolerability. Subjects were primarily Hispanic (94%), and males and females were approximately equally represented (53% and 47%, respectively). There were no Serious Adverse Events (SAEs), severe AEs, or dose-response relationships for overall AEs. The majority of AEs were mild, and all AEs completely resolved by the end of the study. There were no drug-related AEs resulting from clinically significant haematology or clinical chemistry laboratory abnormalities at any dose. In addition, there were no safety issues related to ECGs, vital signs, or physical exam findings. Across the 50 to 400 mg dose range, CD101 plasma exposures were generally dose-proportional, with average C_{max} ranging from 2.76 to 22.7 µg/mL and corresponding $AUC_{0\text{-}168h}$ ranging from 145 to 1160 µg·h/mL. Apparent clearance of CD101 was remarkably low (<0.3 L/hour), and its half-life was long ($t_{1/2}$ >80 h). Excretion of CD101 in urine was minimal (<1%).

Conclusions: CD101 IV was safe and well tolerated as a single dose up to 400 mg, exhibited long plasma $t_{1/2}$, and maintained plasma exposures that support a once-weekly dosing regimen. The overall safety, tolerability and PK profile of CD101 support continued development as a once-weekly therapy for invasive fungal infections.