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P0123 PK/PD analysis suggests the current susceptibility CLSI breakpoint for micafungin and *Candida albicans* is too high

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Background: The current CLSI susceptibility breakpoint for micafungin and *Candida albicans* (0.25 mg/L) is higher than the CLSI ECV (0.03 mg/L). Thus, micafungin may be used against non-wild type isolates with CLSI MICs 0.06-0.25 mg/L, although there are no clinical data to support this. We therefore determined CLSI PK/PD breakpoints for micafungin and *C. albicans* using an *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model.

Materials/methods: Two clinical *C. albicans* with CLSI MICs 0.008 and 0.03mg/L were studied in an *in vitro* PK/PD model (Meletiadis AAC2012) using a 10^3 CFU/mL initial inoculum. Different micafungin exposures with tC_{max} 0.125, 1 and 8 mg/L in 10% human serum and t½=15h were simulated. Drug was added every 24h for 72h and the log_{10}CFU/mL at 72h was associated with micafungin PK/PD indices $tAUC_{0-24}$/MIC using the Emax model. Drug exposure corresponding to a fungistatic effect (i.e no log_{10}CFU/mL reduction compared to the initial inoculum size) that was previously found to correlate with clinical outcome (Andes AAC2011, AAC2008) was calculated. Monte Carlo analysis was then performed simulating a mean±SD of $tAUC_{0-24}$ 96.75±28.93 mg.h/ml attained with the standard dose of 100 mg/kg q24 iv (Mycamine SPC) and the probability of target attainment (PTA) calculated for *C. albicans* isolates with MICs 0.015-8 mg/L.

Results: A 4.2 log_{10}CFU/mL increase was observed in drug free control whereas micafungin reduced initial inoculum by 0.5-0.7 log_{10}CFU/mL with tCmax of ≥1 and 8 mg/L against the isolate with MIC 0.008 and 0.03 mg/l, respectively. A 2-3 log_{10}CFU/ml increase of both isolates was observed with micafungin tCmax of 0.125 mg/L. The *in vitro* PK/PD relationship followed a sigmoid curve (R^2≥0.95) with a mean (95%CI) $tAUC_{0-24}$/MIC associated with stasis of 1342(682-2799). The PTA for these PK/PD targets and the standard dose of micafungin was 100%, 64%, 2% for *C. albicans* isolates with CLSI MICs ≤0.03, 0.06 and ≥0.125 mg/L, respectively.

Conclusions: A weak fungicidal activity was found with micafungin against wild-type isolates. Based on a fungistatic endpoint, the CLSI PK/PD breakpoints of ≤0.03 mg/L was determined. The PK/PD target will not be attained for non-wild type isolates with CLSI MICs 0.06-0.25 mg/L, questioning current CLSI breakpoint for micafungin.