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O1066 *In vivo* pharmacodynamic evaluation of the novel antifungal agent APX001 in a murine model of invasive pulmonary aspergillosis against wild-type and *Cyp51* mutant *Aspergillus fumigatus* strains

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Background: APX001 (active moiety APX001A) is a novel, first-in-class drug targeting the fungal enzyme Gwt1 in the GPI pathway. APX001A has potent, broad *in vitro* and *in vivo* activity against major fungal pathogens including *Aspergillus*. We examined the PD characteristics of APX001 in a neutropenic murine IPA model against multiple AF strains including those with triazole resistance.

Materials/methods: A neutropenic, corticosteroid treated murine model of IPA with 6 AF clinical strains (3 WT, 3 *Cyp51* mutants) were utilized. MECs were determined by CLSI methods. Infection was induced by nasal aspiration. APX001 dosing was by oral route and previously published murine plasma PK was utilized to calculate drug exposures. Dose-fractionation study was performed with AF293 to determine the PK/PD index associated with efficacy. Study duration was 96h and drug efficacy was determined by qPCR of AF DNA from lung homogenates. Efficacy studies for all strains were performed with an APX001 dose range of 5-192 mg/kg/3h. The static and 1-log kill doses were calculated using the sigmoid Emax (Hill) equation and associated PK/PD target AUC/MEC values were determined.

Results: MECs were relatively similar for WT and *Cyp51* mutants (range 0.03-0.06 mg/L). Dose-fractionation revealed AUC/MEC (R^2 0.79) was the most predictive PK/PD parameter. Given the relatively narrow MEC range, the dose-response curves for all strains were relatively congruent. The max kill from beginning of treatment was 1-2 $\log_{10}$ kill for five of six strains. The relationship between AUC/MEC and therapeutic effect for all strains is shown in the figure. The median 24h free drug AUC/MEC that resulted in net stasis and 1-log kill were 48 and 89, respectively.

Conclusions: APX001 demonstrated potent *in vivo* efficacy against WT and triazole resistant AF clinical strains. AUC/MEC was the PK/PD index predictive of efficacy. Net cidal activity was observed for all strains and the exposure-response relationship was relatively steep as free drug AUC/MEC targets for stasis and 1-log kill differed by only 2-fold (48 and 89, respectively). These findings suggest APX001 may be a very useful addition to the antifungal armamentarium given the potent exposure-response relationship observed and novel mechanism of action.