Pharmacokinetics/pharmacodynamics (PK/PD) of the novel, first-in-class glycosylphosphatidylinositol (GPI) inhibitor APX001 in the neutropenic murine invasive candidiasis model against *C. albicans* (CA), *C. glabrata* (CG), and *C. auris* (CAU)

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Introduction & Aim

- Limited treatment options and drug-resistance threaten therapy for invasive candidiasis (IC)
- APX001 (active moiety APX001A) is a novel, first-in-class drug targeting the fungal enzyme *GWT1* in the GPI pathway, leading to pleiotropic effects on cell wall integrity, adherence, pathogenicity, and immune evasion
- **AIM - Examine the PK/PD characteristics of APX001 in the neutropenic murine IC model against multiple *Candida* spp.**

Materials & Methods

Strains and susceptibility testing:
- 5 CA, 5 CG, 4CAU, CLSI methods

Pharmacokinetic studies and analysis:
- Oral dose (range 4-256 mg/kg), plasma PK by LC-MS/MS
- Non-compartmental model

Murine disseminated candidiasis model:
- 6-week-old, female ICR/Swiss mice (23-27 g)
- Neutropenia via cyclophosphamide injection
- 0.1 mL of inoculum (6.3 $\log_{10}$ CFU/mL) injected into lateral tail vein
- Treatment initiated after 2 hours
- Duration 24 h (CA) or 96 h (CG, CAU)
- Treatment effect was determined by CFU counts from kidney homogenates

PK/PD Analyses:

PK/PD index determination
- Dose-fractionation study with CA K1
- Four-fold increasing doses (range 4-1024 mg/kg) of APX001 were fractionated into q3, q6, q8, and q12 h dosing regimens
- Treatment results and associated PK/PD indices AUC/MIC, Cmax/MIC, and T>MIC were modeled to Hill equation and compared by nonlinear regression

PK/PD target studies
- Oral dose range 1-256 mg/kg q6h
- Correlation between efficacy and AUC/MIC was analyzed by nonlinear regression (Hill equation)
- Static and ED_{50} targets were determined

Disclosure: Study was funded by Amplyx Pharmaceuticals

Results

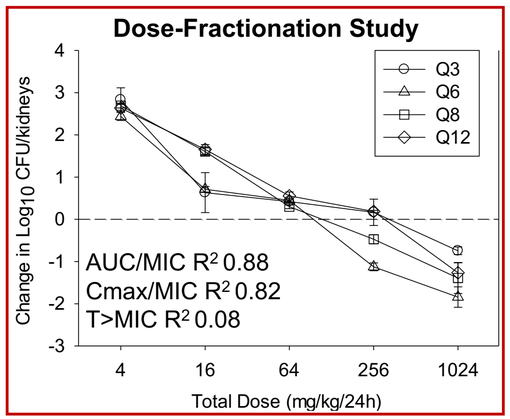
Susceptibility Testing

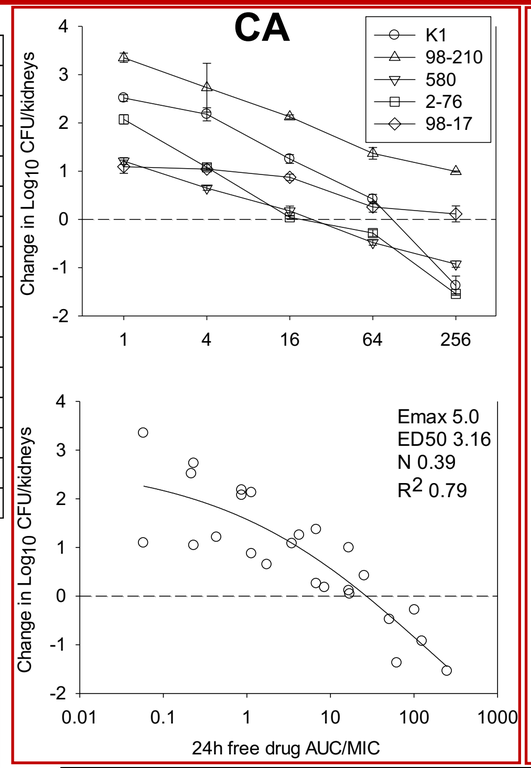
Strain		MIC (mg/L)		
		APX001A	Fluc	Mica
CA	K1	0.008	0.5	0.016
	98-210	0.03	16	0.016
	580	0.004	0.5	0.008
	2-76	0.002	0.25	0.008
	98-17	0.03	16	0.03
CG	10956	0.016	2	0.25
	5592	0.06	32	0.016
	35315	0.016	0.25	0.06
	513	0.03	4	0.016
	5376	0.008	2	0.008
CAU	B11104	0.03	>256	0.25
	B11221	0.008	128	1
	B11219	0.004	>256	4
	B11804	0.008	2	0.5

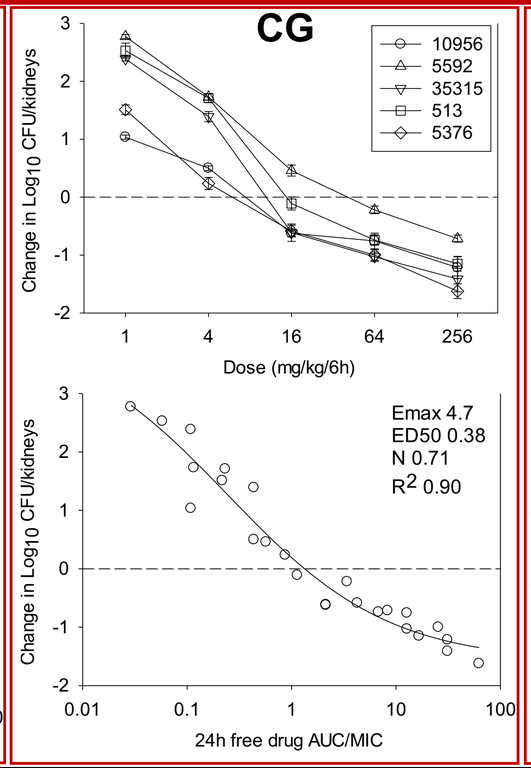
APX001A Murine Pharmacokinetics

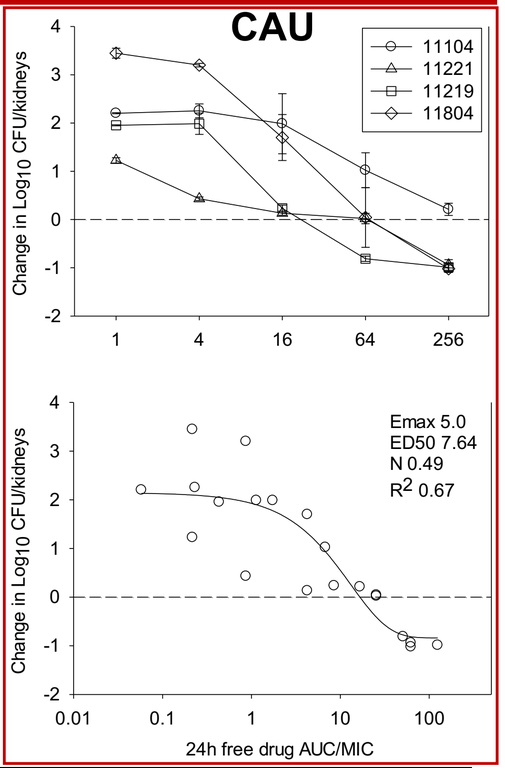
APX001 Oral Dose (mg/kg)	Cmax (mg/L)	$AUC_{0-\infty}$ (mg*h/L)	$T_{1/2}$ (h)
256	15.6	70.0	2.3
64	6.8	27.6	2.8
16	2.02	4.49	2.3
4	0.46	0.87	1.4

Dose-Fractionation Study









Strain		ED_{50}			Stasis		
		24h dose (mg/kg)	24h tAUC/MIC	24h fAUC/MIC	24h dose (mg/kg)	24h tAUC/MIC	24h fAUC/MIC
CA	Mean	41.0	1837	3.67	142.5	10300	20.60
	SD	31.8	1597	3.19	106.7	3248	6.50
CG	Mean	17.7	192	0.38	58.1	656.4	1.31
	SD	10.1	103	0.21	41.3	136.9	0.27
CAU	Mean	212.5	3570.2	7.14	140.7	7336.4	14.67
	SD	307.8	2269.2	4.54	89.5	4150.2	8.30

Conclusions

1] APX001 is a promising novel antifungal agent with potent *in vivo* activity against *C. albicans*, *C. glabrata*, and *C. auris*.
2] APX001A MICs were low and relatively similar across strains, including those resistant to fluconazole and micafungin, consistent with a lack of cross-resistance for a novel mechanism of action molecule.
3] AUC/MIC was the PK/PD index predictive of efficacy based on dose-fractionation analysis
4] Free drug AUC/MIC target for stasis was similar for CA and CAU at 20.6 and 14.7, whereas it was significantly lower for CG at 1.2.
5] These findings support continued clinical development of optimized dosing strategies and susceptibility breakpoint determination for APX001 and APX001A, respectively.