#P423 The Novel Second-Generation IV/Oral Triterpenoid SCY-247 Maintains *In vitro* and *In vivo* Activity against Resistant *Candida glabrata*

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BACKGROUND & OBJECTIVE

- *Candida glabrata* is a major cause of invasive candidiasis and is considered a high priority pathogen by the WHO
- Current therapies are limited by drug-drug interactions (azoles), toxicities (amphotericin B), or the need for IV administration (echinocandins)
- Azole and echinocandin resistance is also of clinical significance
- SCY-247 is a second-generation IV/oral triterpenoid that targets the fungal cell wall by inhibiting glucan synthesis
- *In vitro* activity has translated into *in vivo* efficacy against infections caused by wild-type strains
- We evaluated the *in vitro* activity of SCY-247 and comparators against a panel of echinocandin-resistant clinical *C. glabrata* strains
- The *in vivo* efficacy was also assessed against an azole- and echinocandin-resistant *C. glabrata* strain

MATERIALS & METHODS

- *In vitro* susceptibility testing was performed against 29 echinocandin-resistant clinical strains of *C. glabrata* by CLSI broth microdilution methods
- A *C. glabrata* clinical isolate harboring a Fks1p S629P mutation that was also fluconazole- and echinocandin-resistant (fluconazole, caspofungin, and SCY-247 MICs of 64, >8, & 0.25 mg/L, respectively) was used to establish infection
- Neutropenic ICR mice (N=10/group) were inoculated intravenously, and treatment with vehicle control, SCY-247 (16, 32, & 48 mg/kg PO BID), fluconazole 20 mg/kg PO QD, or caspofungin 5 mg/kg IP QD was initiated 24 hours post-inoculation
- Treatment continued for 7 days, and kidney and lung tissues were collected on day 8 for analysis of fungal burden by colony-forming units (CFU/g)
- Differences in fungal burden were assessed for significance by ANOVA with Tukey's post-test for multiple comparisons

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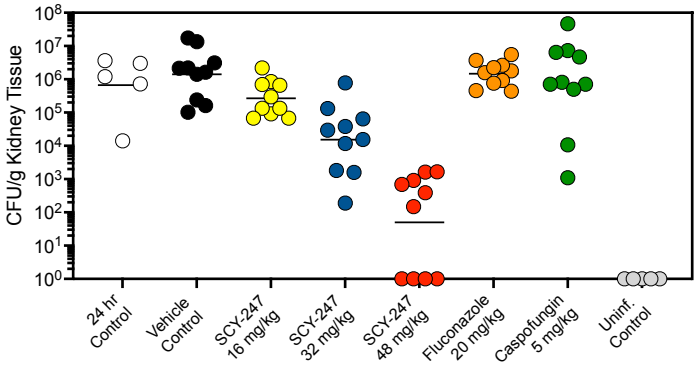
RESULTS

- SCY-247 maintained *in vitro* activity against 24 (MIC ≤0.5 mg/L) of the 29 echinocandin-resistant strains (MIC ranges SCY-247, caspofungin, and micafungin 0.06-4, 0.25->8, and 0.25-4 mg/L, respectively) (**Table 1**)
- This activity was maintained against strains with known Fks1p and Fks2p mutations (e.g., Fks1p – S629P; Fks2p – F,659S, S663P)
- SCY-247 was also efficacious against echinocandin-resistant *C. glabrata* invasive candidiasis
- Dose-dependent reductions in both kidney and lung fungal burdens were observed in mice treated with SCY-247
- Fungal burden within the kidneys was significantly lower in the SCY-247 32 and 48 mg/kg groups (mean range 1.7-4.2 $\log_{10}$ CFU/g) versus placebo (6.2 $\log_{10}$ CFU/g; p≤0.001 for each comparison) (**Figure 1**)
- Lung fungal burden in the SCY-247 32 & 48 mg/kg groups (0-1.5 $\log_{10}$ CFU/g) was also significantly lower versus placebo (4.7 $\log_{10}$ CFU/g; p≤0.001 for both comparisons) (**Figure 2**)
- In contrast, neither fluconazole nor caspofungin led to reductions in fungal burden within either organ (**Figures 1 & 2**)

Table 1. MIC parameters (mg/L) against 29 echinocandin-resistant clinical strains of *C. glabrata*

MIC Parameter	SCY-247	Caspofungin	Micafungin
Range	0.06 - 4	0.25 - >8	0.25 - 4
MIC50	0.25	4	1
MIC90	2	>8	4
GM MIC	0.375	3.08	1.15
Mode	0.25	1	0.5

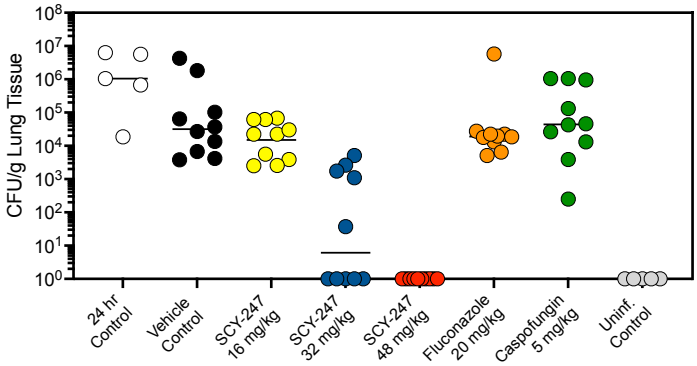
Figure 1. Kidney fungal burden (CFU/g) on day 8 post-inoculation.



Group	24 hour SAC	Vehicle Control	SCY-247 16 mg/kg BID	SCY-247 32 mg/kg BID	SCY-247 48 mg/kg BID	FLU 20 mg/kg QD	CAS 5 mg/kg QD	Uninfect. Control
Mean log CFU/g (SD)	5.83 (0.98)	6.15 (0.75)	5.43 (0.53)	4.19 (1.05) p = 0.0004	1.70 (1.49) p < 0.0001	6.17 (0.37)	5.84 (1.38)	0.0 (0)

p-value vs. Vehicle Control

Figure 2. Lung fungal burden (CFU/g) on day 8 post-inoculation.



Group	24 hour SAC	Vehicle Control	SCY-247 16 mg/kg BID	SCY-247 32 mg/kg BID	SCY-247 48 mg/kg BID	FLU 20 mg/kg QD	CAS 5 mg/kg QD	Uninfect. Control
Mean log CFU/g (SD)	5.93 (1.02)	4.69 (1.05)	4.17 (0.58)	1.50 (1.67) p < 0.0001	0.0 (0) p < 0.0001	4.43 (0.85)	4.70 (1.17)	0.0 (0)

p-value vs. Vehicle Control

CONCLUSIONS & FUNDING STATEMENT

SCY-247 maintained *in vitro* activity against echinocandin-resistant *C. glabrata* and also demonstrated *in vivo* efficacy against invasive candidiasis caused by an echinocandin- and fluconazole-resistant strain. Significant reductions in fungal burden were observed in the kidneys and lungs of mice treated with SCY-247 in a dose dependent fashion. These data support the potential utility of SCY-247 therapy against invasive infections caused by resistant *C. glabrata.*

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