SCY-247, a Novel Second-Generation IV/Oral Triterpenoid Antifungal, Demonstrates *In vitro* Activity Against Fungal Pathogens, Including Azole-Resistant Strains of *Candida* and *Aspergillus*

P2920

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BACKGROUND & OBJECTIVE

- Fungal pathogens are significant causes of morbidity and mortality in at risk patient populations.
- Current approved antifungal treatments are limited by adverse effects/toxicity and increasing resistance.
- SCY-247 (Figure 1) is a second-generation IV/oral triterpenoid antifungal currently under development that inhibits the glucan synthase enzyme responsible for production 1,3-β-D-glucan within the fungal cell wall.
- Our objective was to determine the *in vitro* activity of this agent against different fungal pathogens, including yeast, moulds, and dimorphic fungi that are members of the WHO fungal priority pathogens list.

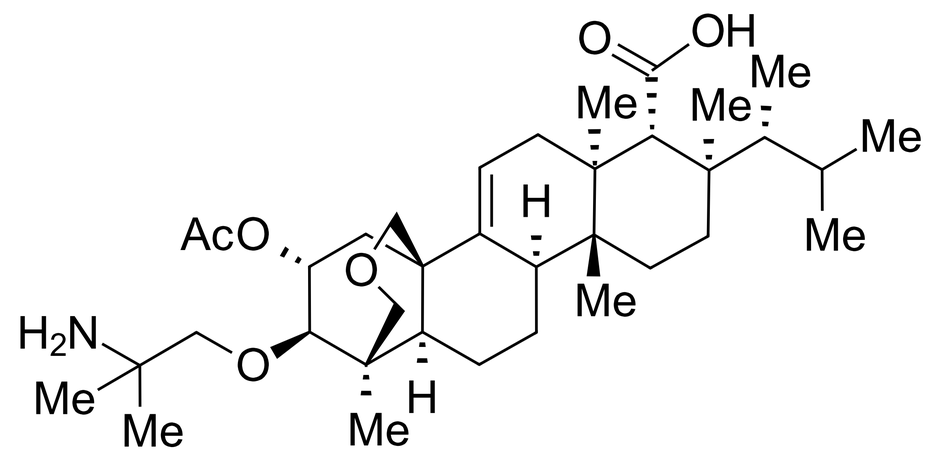
MATERIALS & METHODS

- 155 clinical isolates of yeasts, moulds, and dimorphic fungi were included.
- Antifungal susceptibility testing was performed with SCY-247 (all isolates), and the positive control antifungals fluconazole (*Candida*), voriconazole (*Aspergillus, Fusarium, Scedosporium/Lomentospora, Blastomyces,* and *Histoplasma*), or posaconazole (Mucorales) by CLSI M27 or M38 broth dilution methods.
- MICs for SCY-247 were read at 50% inhibition of growth vs. yeasts and as MEC values against moulds and dimorphic fungi.
- MIC/MEC50/90s, geometric mean (GM) MIC/MECs, and modal MEC/MICs were calculated.

RESULTS

- SCY-247 demonstrated potent *in vitro* activity against *C. albicans, C. auris,* and *C. glabrata* (MIC range 0.06-2 mg/L; GM MIC range 0.21-0.34 mg/L), including fluconazole-resistant strains of *C. albicans, C. auris,* and *C. glabrata* (MIC range 0.125-2 mg/L).
- Activity was also observed against isolates of *C. guilliermondii* (1-2 mg/L), *C. parapsilosis* (0.5-1 mg/L), and *C. neoformans* (4 mg/L).
- Potent activity was also observed against *A. fumigatus* and *A. flavus* (MEC ≤0.03-0.125 mg/L; GM MEC range ≤0.03-0.04 mg/L) including voriconazole resistant *A. fumigatus* (≤0.03 mg/L).
- Similarly, MEC values were low vs. each of the dimorphic pathogens (≤0.03 mg/L), including fluconazole-resistant *Coccidioides* isolates.
- Potency was reduced against *Fusarium* and *Scedosporium/Lomentospora* species (MEC1-16 mg/L; GM MEC 2.52-9.33 mg/L) and the Mucorales (8->16 mg/L).

Figure 1. SCY-247 chemical structure.



Yeasts							
Species (No. Strains)		*C. albicans* (13)	*C. auris* (11)	*C. glabrata* (14)	*C. guilliermondii* (10)	*C. parapsilosis* (10)	*C. neoformans* (12)
SCY-247	Range	0.125-2	0.125-0.5	0.06-2	1-2	0.5-1	4
	MIC50	0.25	0.25	0.125	2	0.5	4
	MIC90	1	0.5	1	2	1	4
	GM MIC	0.34	0.25	0.21	1.74	0.62	4.00
	Mode	0.25	0.25	0.125	2	0.5	4
Fluconazole	Range	0.125->64	1->64	0.25->64	1-16	0.25-2	0.5-64
	MIC50	0.5	2	2	2	0.5	3
	MIC90	>64	>64	64	2	1	16
	GM MIC	1.38	6.22	4.00	2.30	0.50	4.00
	Mode	0.125	2	2	2	0.5	2

Moulds						
Species (No. Strains)		*A. fumigatus* (12)	*A. flavus* (10)	*Fusarium* spp. (10)	*Scedosporium/ Lomentospora* (13)	Mucorales (10)
SCY-247	Range	≤0.03-0.125	≤0.03	4-16	1-8	8->16
	MEC50	≤0.03	≤0.03	8	2	8
	MEC90	0.06	≤0.03	16	4	32
	GM MIC	0.04	≤0.03	9.33	2.52	11.0
	Mode	≤0.03	≤0.03	8	2	8
Voriconazole / Posaconazole (Mucorales)	Range	0.25->16	0.25-2	4->16	0.5->16	≤0.03->16
	MIC50	0.5	0.75	12	2	1
	MIC90	4	1	32	2	26.4
	GM MIC	0.89	0.57	10.6	1.23	0.88
	Mode	0.5	0.25	4	2	0.5

Dimorphics				
Species (No. Strains)		*B. dermatitidis* (10)	*Coccidioides* spp. (10)	*H. capsulatum* (10)
SCY-247	Range	≤0.03	≤0.03	≤0.03
	MEC50	≤0.03	≤0.03	≤0.03
	MEC90	≤0.03	≤0.03	≤0.03
	GM MIC	≤0.03	≤0.03	≤0.03
	Mode	≤0.03	≤0.03	≤0.03
Voriconazole / Fluconazole (*Coccidioides*)	Range	0.03-0.125	4->64	0.03-0.125
	MIC50	0.06	8	≤0.03
	MIC90	0.125	>64	0.125
	GM MIC	0.08	11.3	0.05
	Mode	0.125	8	≤0.03

SCY-247 was provided by SCYNEXIS, Inc. This study was supported by DMID/NIAID/NIH under Contract Nos. HHSN272201700039I (Task Order A65) and 75N93019D00022 (Task Order A22)

CONCLUSIONS

SCY-247 demonstrates potent *in vitro* activity against a broad range of pathogenic fungi. The most potent activity was observed against *Candida* and *Aspergillus* species and the dimorphic fungi *B. dermatitidis, H. capsulatum,* and *Coccidioides* species. Further studies are warranted to determine if the *in vitro* activity translates into *in vivo* efficacy.