

The novel second-generation IV/oral triterpenoid SCY-247 is efficacious in an experimental murine model of invasive candidiasis caused by *Candida glabrata*

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# Disclosures

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- bioMerieux
- Bruker
- F2G
- Mycovia
- Scynexis
- Sfunga

## Collaborations through NIH

- Amplyx
- F2G
- Fujifilm/Toyama/Appili
- Scynexis
- Mycovia

Member, CLSI Antifungal Susceptibility Subcommittee

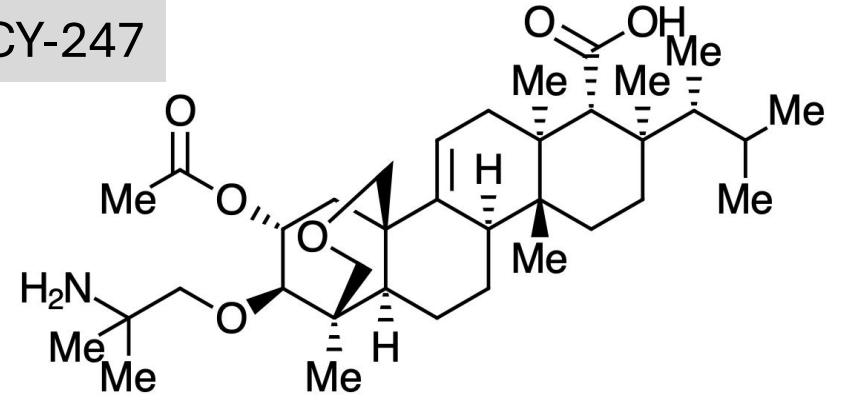
- *Candida glabrata* (*Nakaseomyces glabratus*) identified as a priority fungal pathogen by WHO
- 2<sup>nd</sup> most common *Candida* species cultured from patients with invasive disease at many institutions
- Reduced susceptibility to fluconazole
- Elevated rates of echinocandin resistance reported at some institutions

Critical group	High group	Medium group
 <i>Cryptococcus neoformans</i>	 <i>Nakaseomyces glabrata</i> ( <i>Candida glabrata</i> )	 <i>Scedosporium</i> spp.
 <i>Candida auris</i>	 <i>Histoplasma</i> spp.	 <i>Lomentospora prolificans</i>
 <i>Aspergillus fumigatus</i>	 Eumycetoma causative agents	 <i>Coccidioides</i> spp.
 <i>Candida albicans</i>	 Mucorales	 <i>Pichia kudriavzevii</i> ( <i>Candida krusei</i> )
	 <i>Fusarium</i> spp.	 <i>Cryptococcus gattii</i>
	 <i>Candida tropicalis</i>	 <i>Talaromyces marneffeii</i>
	 <i>Candida parapsilosis</i>	 <i>Pneumocystis jirovecii</i>
		 <i>Paracoccidioides</i> spp.

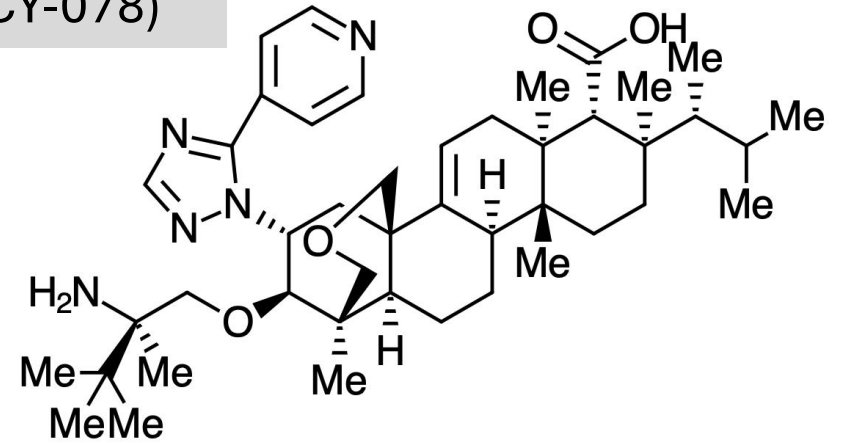
# SCY-247

- Semi-synthetic derivative of natural product
- Potent (1,3)- $\beta$ -D-glucan synthase inhibitor (GSI)
  - Same target as echinocandin antifungals
  - 2<sup>nd</sup> member of a new class of antifungals  
(triterpenoid – same class as ibrexafungerp [SCY-078])
- Broad-spectrum demonstrated against limited number of *Candida* species, *Aspergillus* species, *Coccidioides immitis*, and *Histoplasma capsulatum*
- *In vivo* activity demonstrated against disseminated candidiasis caused by *C. albicans*
- Being developed for oral and IV administration (Scynexis)

SCY-247



Ibrexafungerp  
(SCY-078)



# Objective

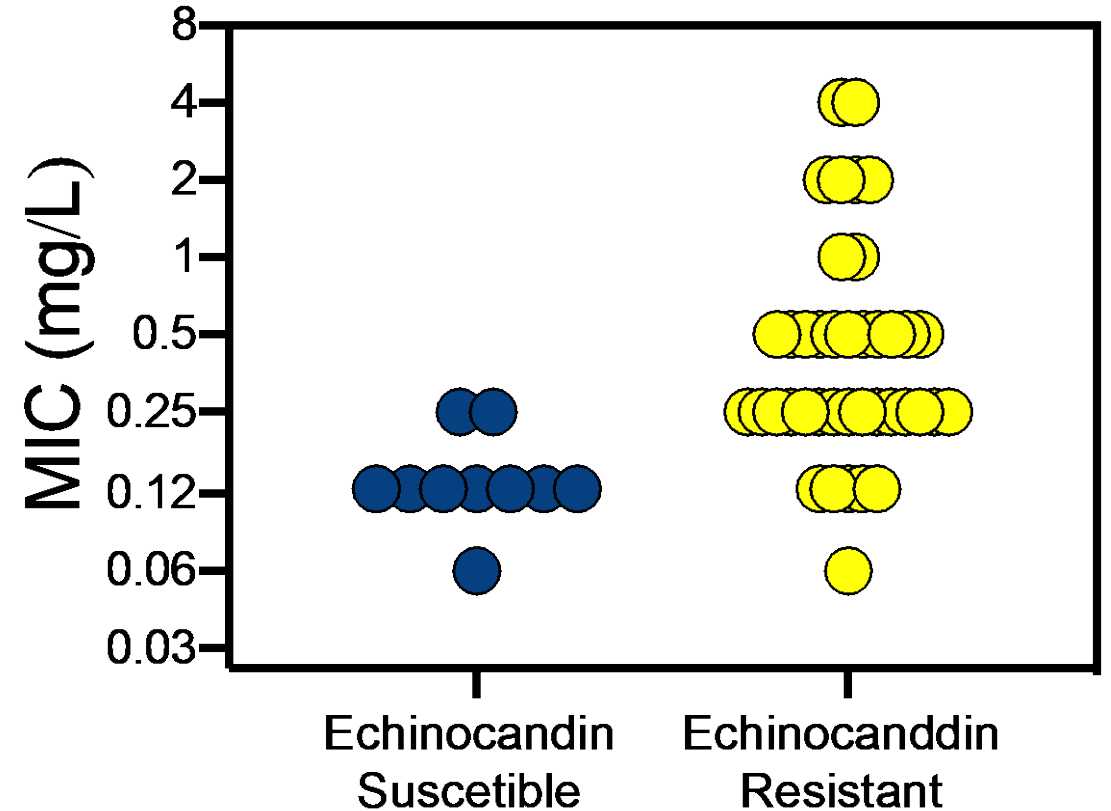
- Evaluate the activity of SCY-247 against *Candida glabrata*
  - *In vitro* activity against wild-type and resistant *C. glabrata* (including strains with defined *FKS* point mutations)
  - *In vivo* activity in an established murine model of disseminated candidiasis

# Methods – *In vitro* Activity

- CLSI M27ed4 broth microdilution method
  - >50% inhibition of growth at 24 hours at 35°C
- 50 *Candida glabrata* clinical isolates
  - Submitted to the UT Health San Antonio Fungus Testing Laboratory for clinical diagnostic testing
  - 10 echinocandin-susceptible isolates
  - 40 echinocandin-resistant isolates

# Results – *In vitro* Activity

MIC Parameter	Echinocandin Susceptible	Echinocandin Resistant
MIC Range	0.06 – 0.25	0.06 - 4
MIC <sub>50</sub>	0.125	0.25
MIC <sub>90</sub>	0.25	0.5
GM MIC	0.133	0.406
Mode	0.125	0.25



# Methods – Infection Model

- Neutropenic male ICR mice
  - 5-fluorouracil 5 mg/mouse IV 1 day prior to IV infection
- Infecting organism – *C. glabrata* 05-761
  - Echinocandin-susceptible clinical isolate
  - IV inoculation

Agent	SCY-247 50% inhibition	SCY-247 100% inhibition	Fluconazole 50% inhibition	Caspofungin 50% inhibition
MIC (mg/L)	0.125 mg/L	0.5 mg/L	4 mg/L	0.1245 mg/L

- Fungal burden – Treatment initiated 1 day post challenge and continued through day 7
  - Kidneys and lungs collected on day 8
  - Fungal burden assessed by measured CFU/g tissue

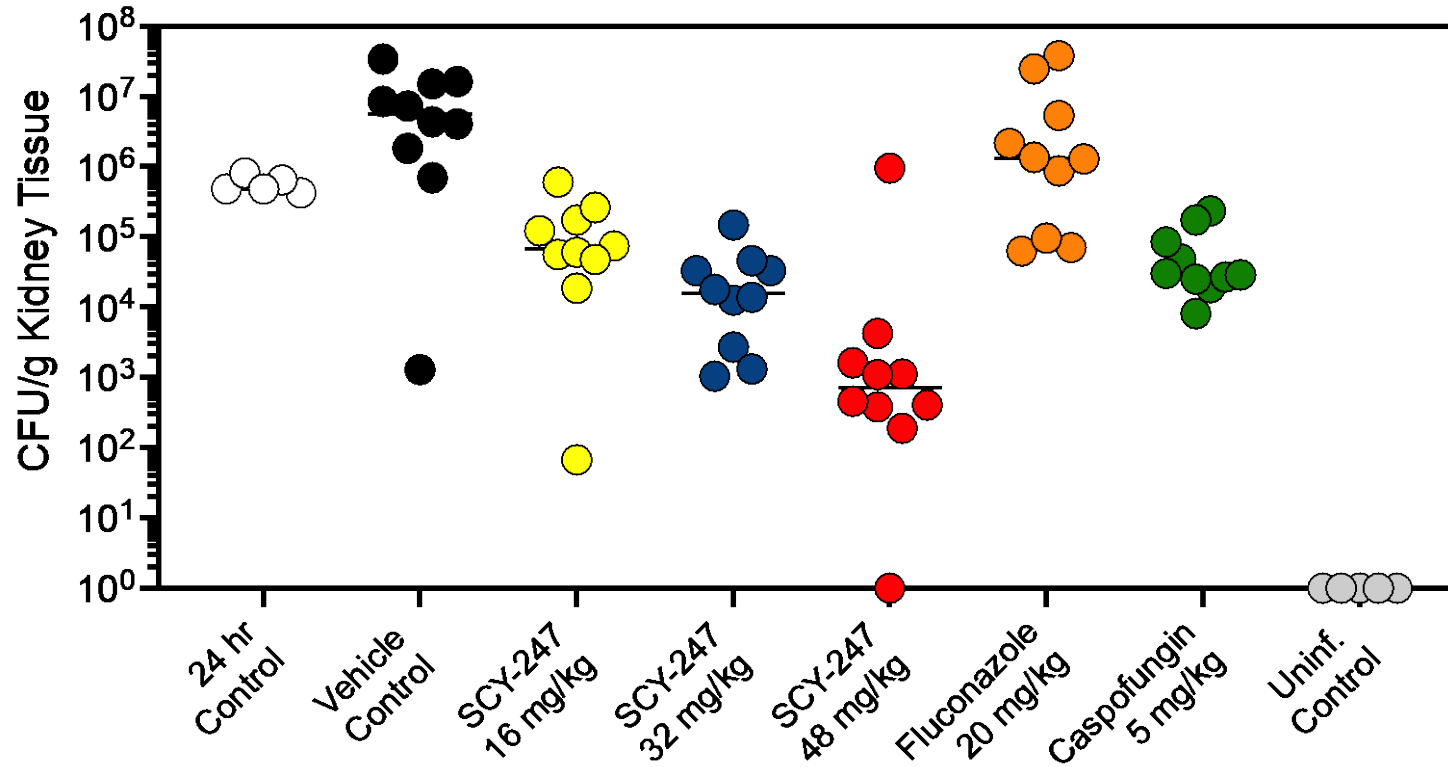


# Methods – Infection Model

- Treatment Groups

- 24-hour fungal burden
- Vehicle control – 0.5% w/v methyl cellulose
- SCY-247 16 mg/kg orally twice daily
- SCY-247 32 mg/kg orally twice daily
- SCY-247 48 mg/kg orally twice daily
- Fluconazole 20 mg/kg orally twice daily
- Caspofungin 5 mg/kg by intraperitoneal injection once daily

# Results – *In vivo* Activity

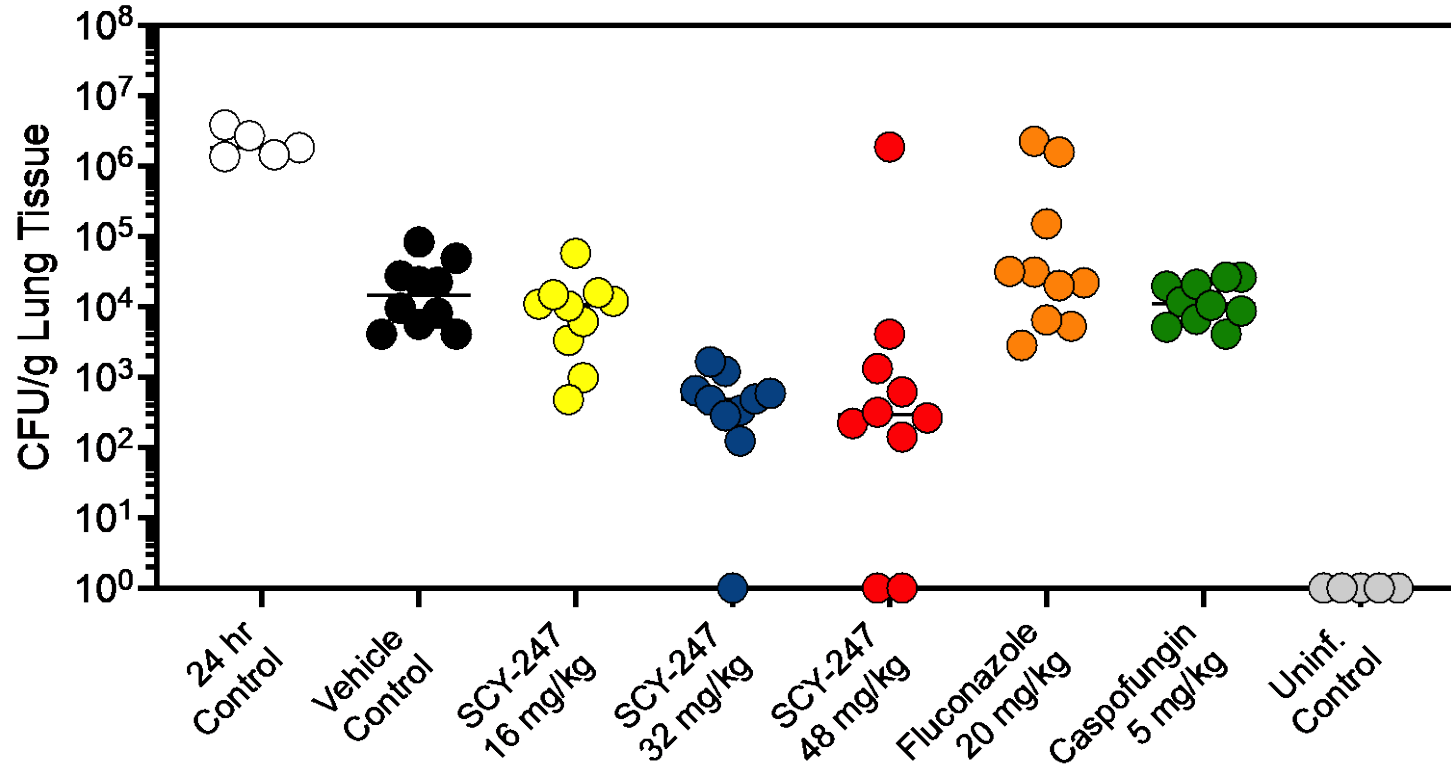


- Significant and dose-dependent reductions in kidney fungal burden observed with SCY-247
  - Reductions vs. 24 hr control 1.14-2.84 log<sub>10</sub> CFU/g
  - Cidal activity
- Significant reductions also observed with caspofungin

Group	24-hour Control	Vehicle Control	SCY-247 16 mg/kg BID	SCY-247 32 mg/kg BID	SCY-247 48 mg/kg BID	Fluconazole 20 mg/kg QD	Caspofungin 1 mg/kg QD	Uninfect. Control
Mean log CFU/g (SD)	5.74 (0.11)	6.42 (1.26)	4.6 (1.08) p = 0.0016	4.090 (0.70) p < 0.0001	2.90 (1.46) p < 0.0001	6.08 (0.99)	4.62 (0.45) p = 0.011	0.0 (0)

p-value vs. Vehicle Control

# Results – *In vivo* Activity



- Significant and dose-dependent reductions in lung fungal also burden observed with SCY-247
  - Reductions vs. vehicle control 0.34-1.73 log<sub>10</sub> CFU/g
  - Cidal activity with SCY-247 16 and 32 mg/kg doses
- No reductions observed with caspofungin

Group	24-hour Control	Vehicle Control	SCY-247 16 mg/kg BID	SCY-247 32 mg/kg BID	SCY-247 48 mg/kg BID	Fluconazole 20 mg/kg QD	Caspofungin 1 mg/kg QD	Uninfect. Control
Mean log CFU/g (SD)	6.31 (0.19)	4.16 (0.46)	3.82 (0.61)	2.43 (0.91) p = 0.0007	2.52 (1.78) p = 0.0014	4.63 (0.99)	4.06 (0.29)	0.0 (0)

p-value vs. Vehicle Control

# Summary and Future Steps

- SCY-247 was effective at reducing fungal burden
  - Significant reductions occurred in both the kidneys and lungs of neutropenic mice infected with an echinocandin susceptible strain of *C. glabrata*
  - Cidal activity ( $>1 \log_{10}$  reduction in CFU counts) achieved
- *In vivo* results consistent with the *in vitro* activity observed against the clinical strain used to establish infection and against other clinical isolates of *C. glabrata*
- **Next step** – *in vivo* model of disseminated infection caused by an echinocandin-resistant clinical isolate

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