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In vitro Interaction between SCY-078, Echinocandins and Azoles against Susceptible & Resistant *Candida* spp. Determined by the Checkerboard Method

SCYNEXIS, Inc.
Tel. 201-884-5485
info@scynexis.com

K. Borroto-Esoda[1]; B. Scorneaux, PhD[1]; S. Helou, MD[1] and D. Angulo, MD[1]

[1]SCYNEXIS, Inc, Jersey City, NJ.

INTRODUCTION

SCY-078 is a novel intravenous and oral triterpenoid antifungal agent currently in clinical development for the treatment of both invasive and mucocutaneous fungal infections, with:

- Broad-spectrum activity vs. both *Candida* and *Aspergillus*
- Fungicidal activity vs. *Candida*
- Extensive tissue distribution, making it a suitable candidate for multiple indications including systemic, pulmonary and vulvovaginal infections.

SCY-078 is a glucan synthase inhibitor (GSI) with a novel chemical structure distinct from other GSI (i.e. echinocandins). We evaluated the *in vitro* antifungal activity of SCY-078 alone and in combination with other anti-fungal agents against a panel of *Candida* isolates.

METHODS

The *in vitro* activity of SCY-078 was evaluated alone and in combination with echinocandins, (caspofungin, micafungin and anidulafungin) and azoles (fluconazole, ketoconazole, itraconazole, voriconazole and posaconazole) against a panel of *Candida* isolates (ATCC):

- *C. albicans* 90028, a fluconazole-susceptible isolate
- *C. albicans* MYA-2732, a fluconazole-resistant isolate
- *C. glabrata* 90030
- *C. parapsilosis* 90018

Minimal inhibitory concentrations (MIC) of the compounds alone and in combination were determined using a broth microdilution method in accordance with CLSI M27-A3 guidelines.

MIC endpoints (80% inhibition) were quantified using a spectrophotometric method after 24 hours of incubation at 35°C (25°C for *C. glabrata*).

- The effect of combination testing was reported according to a Fractional Inhibitory Concentration Index (FICI), which assigns a numerical value (formula below) to the interaction of the two compounds.
- FICI interpretation:
  - Synergistic FICI ≤ 0.5
  - Additive FICI > 0.5 but ≤ 4.0*
  - Antagonistic FICI > 4.0

* Additive is also referred to as indifferent .

RESULTS

FICI values for SCY-078 in combination with azoles ranged from 0.96 to 1.40 (additive interaction).

MIC [geometric mean*] vs. *C. albicans 90028*

	Alone		Combination		
SCY-078 +Azole	SCY-078	Azole	SCY-078	Azole	FICI
Fluconazole	0.40	0.25	0.20	0.19	1.25
Ketoconazole	0.35	0.13	0.19	0.06	1.04
Itraconazole	0.35	1	0.18	0.9	1.40
Voriconazole	0.5	0.08	0.25	0.04	0.96
Posaconazole	0.5	0.25	0.13	0.25	1.25

*n=4

MIC [geometric mean*] vs. C. *parapsilosis 90018*

	Alone		Combination		
SCY-078 +Azole	SCY-078	Azole	SCY-078	Azole	FICI
Fluconazole	0.5	0.5	0.25	0.25	1
Ketoconazole	0.5	0.13	0.25	0.09	1.20
Itraconazole	0.5	2	0.25	1	1
Voriconazole	1	0.0625	0.5	0.03125	1
Posaconazole	0.5	0.5	0.25	0.25	1

*n=4

MIC [geometric mean*] vs. *C. glabrata 90030*

	Alone		Combination		
SCY-078 +Azole	SCY-078	Azole	SCY-078	Azole	FICI
Fluconazole	0.90	4	0.5	4	1.56
Ketoconazole	1	4	0.5	4	1.50
Itraconazole	1	4	0.5	2	1
Voriconazole	1	0.06	0.5	0.03	1
Posaconazole	0.90	1	0.43	0.5	0.97

*n=4

SCY-078 exhibited additive antifungal activity in combination with caspofungin, micafungin and anidulafungin against both the fluconazole susceptible and resistant *C. albicans* strains.

MIC [geometric mean*] vs. *C. albicans 90028*

	Alone		Combination		
SCY-078 + Echinocandin	SCY-078	Echinocandin	SCY-078	Echinocandin	FICI
Caspofungin	0.33	0.20	0.14	0.09	0.88
Micafungin	0.40	0.10	0.16	0.03	0.68
Anidulafungin	0.24	010	0.18	0.04	0.64

*n=4

MIC [geometric mean*] vs. *C. albicans MYA-2732*

	Alone		Combination		1.04
SCY-078 + Echinocandin	SCY-078	Echinocandin	SCY-078	Echinocandin	FICI
Caspofungin	0.24	0.28	0.05	0.13	0.65
Micafungin	0.16	0.23	0.06	0.09	0.75
Anidulafungin	0.16	0.05	0.06	0.03	0.82

*n=4

CONCLUSION

No antagonistic interactions were observed between SCY-078 and echinocandins or azoles. These data suggest that SCY-078 can be combined with other antifungals to manage *Candida* spp. infections.