Poster #45

SCY-078 Displays Potent In-Vitro Activity Against Candida glabrata Isolates with Mutations in fks Gene

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SCYNEXIS

Background

- The clinical incidence of resistance to approved antifungal drugs is increasing, particularly among C. glabrata strains.
- Resistance to echinocandins (ECH) in this organism is usually caused by point mutations in hot spot (HS) regions of the *fks* gene encoding the 1,3-β-D-glucan synthase (GS).
- Clinically, the presence of fks mutations in C. glabrata is associated with higher rates of treatment failure^a and mortality^b.
- SCY-078 is an orally bioavailable 1,3-β-D-glucan synthesis inhibitor (GSI) that shares the same mechanism of action with ECHs but is structurally distinct.
- SCY-078 has the potential for unique activity profiles because it is the first-in-class of structurally novel triterpene antifungals in clinical development for the treatment of candidemia and invasive candidiasis.
- Here we report the *in vitro* activity of SCY-078 against *C. glabrata* strains with mutations in *fks*.

Methods

- In vitro MIC data (50% inhibition at 24 hrs) for SCY-078 against C. glabrata isolates with fks mutations were compiled from across 3 independent studies.
- The combined studies included 48 C. glabrata isolates with fks mutations and 105 wild-type (WT) C. glabrata isolates as controls.
- Across the three studies, in vitro susceptibility was determined by broth micro-dilution using CLSI methods (M27-S3).
- Resistance to SCY-078 was defined as MIC values ≥2 μg/mL
- Resistance to CASP and MICA was defined as MIC values ≥0.5 and ≥ 0.25 µg/mL respectively
- Comparator compounds varied by study; all three studies included caspofungin (CASP), one study included micafungin (MICA).

Results Summary

- In vitro MIC₅₀ values for SCY-078 against WT C. glabrata strains ranged from 0.25 to 0.5 µg/mL across the 3 studies.
- For WT isolates the MIC₅₀ values for CASP ranged from 0.06 to 0.12 μg/mL; the MICA MIC₅₀ value was 0.03 μg/mL (N=67).
- Among the 48 isolates with mutations in *fks*; 20 had mutations in *fks*1 (HS1) at positions F625, S629, L6301, D632, S645 and 28 had mutations in *fks*2 (HS1) at positions D648, F659, L662, S663, L664, D666, P667, and/or P1371 (HS2).
- SCY-078 was active (MIC values similar to WT) against 33/48 (69%) of the C. glabrata isolates with fks mutations.
- By contrast, among C. glabrata isolates with fks mutations, CASP and MICA were only active against 10/48 (20%) and 11/25 (44%) isolates, respectively.

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Activity of SCY-078 and Comparators Against fks1 Mutant Strains

	CLSI MIC by Study (µg/mL)ª				
Mutation (N)	SCY-078	CASP	MICA ^c		
WT ^b	0.5, 0.5, 0.25	0.06, 0.125	0.03		
F625S (3)	1, 2, 4	0.06, 1, 2	0.03		
F625Y (2)	0.5. 0.5	0.06, 0.125	0.03		
S629P (5)	1 (1), 0.5, 1(1)	8 (8), 16, 16 (8)	2 (2)		
L630I (2)	0.5, 0.5	0.12, 0.125	0.008		
D632G (3)	1, 1 (4)	2, 2 (16)	ND		
D632V (1)	0.5	0.25	0.03		
D632Y (2)	4 , 0.5	1, 0.25	0.125		
S645P (1)	1	2	1		
R631S/S629P (1)	1	0.5	0.06		
*If the mutation is represented by more than one isolate in a study the MIC for additional isolates are in parenthesis. Values in RED FONT indicate resistance					
^b MIC values represent the MIC _{so} for the WT population in each study					
SMICA was only evaluated in one study					
ND – Not Determined					

Activity of SCY-078 and Comparators Against fks2 Mutant Strains

	CLSI MIC by Study (µg/mL)ª					
Mutation (N)	SCY-078	CASP	MICAc			
WT ^b	0.5, 0.5, 0.25	0.06 - 0.125	0.03			
D648E (2)	1, 0.5	0.25, 0.125	0.06			
F659del (2)	16, 2	16, 16	2			
F659S (2)	4, 0.5	2, 16	0.25			
F659V (3)	2, 2, 2	0.5, 4, 1	0.125			
F659Y (1)	1	2	0.25			
L662W (1)	4	2	1			
S663F (3)	0.5 (0.25), 0.5	0.5 (0.25), 0.5	0.5 (0.125)			
S663P (6) ^d	1, 1, 1, <mark>2, 2, 4</mark>	0.5, 0.5, 0.5, 2, 4, 16	0.25, 0.5, 1, 1, 2, 4			
S663P (3) ^d	0.5, 1 (2)	16, 16 (16)	ND			
L664R (1)	1	1	ND			
P667T (1)	0.5	2	ND			
D666E (1)	0.25	2	ND			
P1371S (HS2, 1)	0.125	0.03	0.03			
D666E,K753Q (1)	0.25	0.5	0.06			
If the mutation is represented by more than one isolate in a study the MIC for additional isolates are in parenthesis. Values						
^b MIC values represent the MIC ₅₀ for the WT population in each study						
MICA was only evaluated in one study						
"9 isolates contained the 5663P mutation; 6 from one study and three from the remaining two studies ND = Not Determined						

The most commonly observed ECH-R mutation is the <u>S663P</u> in fks2^c SCY-078 remained active against the majority of strains with the S663P mutation: MIC <2 μ g/mL

SCY-078 Demonstrated Superior Activity Compared to ECH Against Isolates with *fks* Mutations Across Three Studies.



Phenotype	MIC _{s0} (range [µg/ml]):			
(no. of isolates)	SCY-078	Caspofungin	Micafungin	
WT (67)	0.5 (0.12 - 16)	0.06 (0.03 - 16)	0.03 (0.008 - 4)	
fks (25)	1 (0.12 - 16)	0.5 (0.03 - 16)	0.25 (0.008 - 4)	
Fold ∆ in MIC ₅₀	2	8.3	8.3	
WT (9)	0.25 (0.12 -0.5)	0.06 (0.06 - 1)	ND	
fks (11)	1 (0.25 – 4)	4 (2 – 16)	ND	
Fold ∆ in MIC ₅₀	4	>20	NA	
WT (29)	0.5 (0.5 - 2)	0.12 (0.03 - 16)	ND	
fks (12)	1 (0.5 – 2)	1 (0.12 - 16)	ND	
Fold ∆ in MIC ₅₀	2	8.3	NA	

Conclusions

SCY-078 demonstrated superior *in vitro* activity as compared to CASP and MICA against *C. glabrata* isolates with *fks* mutations. These results suggest that SCY-078 may be a suitable option for the treatment of infections caused by echinocandin-resistant *C. glabrata* strains.

References

"Alexander et.al., CID 2013, bFarmakiotis et.al., Emerging Infectious Diseases 2014, "Perlin, CID 2015