Poster #45

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

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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* MIC_{50} 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 MIC_{50} values for CASP ranged from 0.06 to 0.12 μg/mL; the MICA MIC_{50} 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, L630I, 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.

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

[a]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_{50} for the WT population in each study
[c]MICA was only evaluated in one study
ND – Not Determined

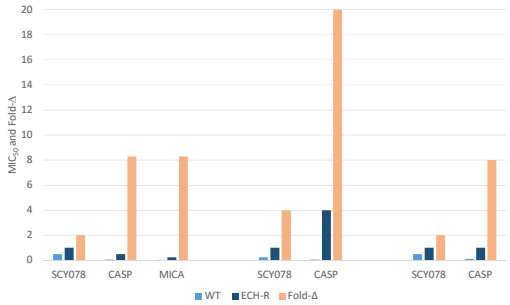
Activity of SCY-078 and Comparators Against *fks2* Mutant Strains

	CLSI MIC by Study (μg/mL)[a]		
Mutation (N)	SCY-078	CASP	MICA[c]
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, 2, 2, 4	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

[a]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_{50} for the WT population in each study
[c]MICA was only evaluated in one study
[d]9 isolates contained the S663P mutation; 6 from one study and three from the remaining two studies
ND = Not Determined

The most commonly observed ECH-R mutation is the S663P in fks2[c]
SCY-078 remained active against the majority of strains with the S663P mutation: MIC <2 μg/mL

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



Phenotype (no. of isolates)	MIC_{50} (range [μg/ml]):		
	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 Δ 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 Δ 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 Δ 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
[a]Alexander et.al., CID 2013, [b]Farmakiotis et.al., Emerging Infectious Diseases 2014,
[c]Perlin, CID 2015

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