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Activity of SCY-078 against Candida spp. obtained by EUCAST and CLSI procedures

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Background: We studied the antifungal activity of SCY-078 (an orally bioavailable 1,3-beta-D-glucan synthesis inhibitor), micafungin (MYC) and fluconazole (FLC) against 178 yeasts isolates causing fungemia in patients recently admitted to a large European hospital in Madrid, Spain.

Material/methods: Antifungal susceptibility testing was performed according to the microdilution broth procedures CLSI M27-A3 and EUCAST EDef 7.3. MIC for the three drugs was defined as the lowest concentration of drug that resulted in visual inhibition of ≥50% of growth in comparison to growth in a drug-free control. Values achieving statistical significance are in **bold** (P<0.05).

Results: SCY-078 and MYC showed potent *in vitro* activity against the isolates as shown by the low MIC values (in µg/ml obtained by CLSI and EUCAST, respectively [FLC (0.712 vs 1.253), MYC (0.041 vs. 0.079, SCY-078 (0.137 vs. 0.270)]. SYC-078 demonstrated significantly lower MIC values than MYC against *C. parapsilosis* and non-*Candida* isolates. By contrast, MYC demonstrated significantly lower MIC values for the remaining species. SCY-078 and MYC showed attenuated activity against the *Candida* isolates with mutations in the *fks* genes compared to wild-type isolates. However, the MIC_{50} of MYC against echinocandin-resistant isolates increased a mean of 15 fold-Δ (ratio of each individual MIC/MIC_{50} of the overall wild-type isolates) (range 4 - 133) compared to the wild-type isolates. By contrast, the individual MICs of SCY-078 only increased by a mean of 2 fold-Δ (range 1 - 32). Individual mutations in *fks* genes had different effects on the two compounds activity.

CLSI M27-A3 (GM)	FLC (CLSI)	FLC (EUCAST)	MYC (CLSI)	MYC (EUCAST)	SCY-078 (CLSI)	SCY-078 (EUCAST)

C. albicans (55)	0.178/	0.273	**0.008**	**0.016**	**0.029**	**0.065**
C. parapsilosis (33)	0.422	0.5	**0.458**	**0.656**	**0.206**	**0.266**
C. glabrata (31)	2.287	7.153	**0.011**	**0.030**	**0.168**	**0.365**
C. tropicalis (8)	0.25	0.353	0.035	0.051	0.066	0.353
C. krusei (12)	10.07	22.627	**0.051**	**0.06**	**0.395**	**0.445**
Other *Candida* spp. (26)	1.026	1.205	**0.036**	**0.053**	**0.369**	**0.556**
Non-*Candida* (13)	10.886	20.88	**9.33**	**11.61**	**4.66**	**7.19**
FLC-R *Candida* isolates (24)	19.5	24.6	**0.043**	**0.049**	**0.291**	**0.423**
fks-mutant *Candida* isolates (9)	0.925	1.714	0.169	0.734	0.338	0.793

We did not find cross-resistance between SCY-078 and FLC in the panel of FLC-resistant isolates. Overall essential agreement between CLSI and EUCAST was 90.3%. However, the agreement was higher for *C. albicans, C. parapsilosis* and non-*Candida* than for *C. tropicalis* and other *Candida* spp.

Conclusions: SCY-078 is a promising drug with high antifungal activity against *Candida* isolates. CLSI and EUCAST standard procedures were comparable and suitable for antifungal susceptibility testing of this compound.