Candida auris is Highly *In Vitro* Susceptible to Ibrexafungerp (formerly SCY-078) in EUCAST Antifungal Susceptibility Testing

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Objectives: *Candida auris* is a multidrug-resistant yeast rapidly emerging as a significant cause of nosocomial infections. Here, we report the susceptibility of *C. auris* to the new oral antifungal drug candidate ibrexafungerp (formerly SCY-078); a synthetic enfumafungin derivative inhibiting glucan synthase. It is active against *Candida*, *Aspergillus* and *Pneumocystis* and is currently in clinical development for mucocutaneous and invasive fungal infections.

Methods: EUCAST AFST according to E.Def 7.3.1 was performed on 122 clinical *C. auris* isolates (from India (n=120) and Oman (n=2)) and three *C. auris* control strains JCM15448, KCTC17809 and KCTC17810; 16 Danish clinical *C. albicans* and 16 *C. glabrata* isolates and the control strains *C. albicans* ATCC64548, *C. krusei* ATCC6258 and *C. parapsilosis* ATCC22019. Cell-culture treated microtitre plates (Nunc, Thermo Fisher Scientific, cat. no. 167008) were prepared using the ISO method. The MICs were compared to previously published MICs for anidulafungin (ANF), micafungin (MCF), amphotericin B (AMB), fluconazole (FLU), isavuconazole (ISA), itraconazole (ITR), posaconazole (PRC) and voriconazole (VOR).

Results: The *in vitro* activity of ibrexafungerp (IBX) against *C. auris* was uniform with MICs displaying a Gaussian distribution spanning 0.06-2 mg/L suggesting an equal efficacy across the 122 isolates (Table). The modal MIC and MIC_{50} were 0.5 mg/L. For the *C. auris* reference strains, the MICs were 0.06 mg/L, 0.125 mg/L and 0.5 mg/L, respectively. In contrast, MIC distributions for anidulafungin, micafungin, isavuconazole, voriconazole, itraconazole and posaconazole were wide (spanning 10-13 dilutions) suggesting differential activity against the isolates. Of note, ibrexafungerp MICs remained low (MICs of 0.25 mg/L and 0.5 mg/L) for the isolates resistant to anidulafungin and micafungin (MICs >32 mg/L). Finally, fluconazole MICs for all but one isolate were 16- >256 mg/L suggesting almost universal fluconazole resistance whereas the amphotericin B MICs clustered close to the non-species-specific breakpoint of 1 mg/L. Subsequently, ibrexafungerp activity was compared for *C. albicans, C. glabrata* and *C. auris*. MIC_{50}, (range) were 0.06 mg/L (0.03-0.125 mg/L), 0.25 mg/L (0.25-0.5 mg/L) and 0.5 mg/L (0.06-2 mg/L), respectively.

Conclusion: Ibrexafungerp, a novel oral glucan synthase inhibitor, shows promising *in vitro* activity against *C. auris* suggesting it may be a welcomed therapeutic against this emerging threat with few treatment options. Ibrexafungerp's MICs were in general one step higher against *C. auris* than against *C. glabrata* and remained sensitive against isolates with antifungal resistance, including vs. highly echinocandin-resistant *C. auris* isolates.

Table. MICs (mg/L) of ibrexafungerp (IBX) and comparator antifungals against 122 clinical *C. auris* isolates. The MIC_{50} is highlighted in bold and the modal MIC is underscored. Off-scale MICs are shown in the first concentration outside the tested range.

	0.004	**0.008**	**0.016**	**0.03**	**0.06**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**>32/64**	**128**	**256**	**>256**
IBX					1	3	33	**63**	20	2								
ANF			1	11	35	**30**	12	12	11	2	1				7			
MCF				5	30	**70**	9								8			
AMB								14	**108**									
FLU									1				4	10	6	14	**33**	54
ISA	20	1	1	19	9	**19**	21	21	6	5								
VOR	1			1	1	16	13	**34**	38	13	5							
ITR	2	2	9	5	14	**34**	36	19	1									
PRC	1	8	24	**39**	35	11	3	1										