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. Ibrexafungerp (formerly SCY-078) is a novel oral synthetic enfumafungin derivative inhibiting glucan synthase. It is active *in vitro* and in animal models against *Candida*, *Aspergillus* and *Pneumocystis* and is currently in clinical development for mucocutaneous and invasive fungal infections. Here, we investigate the susceptibility of *C. auris* to ibrexafungerp compared to that of eight comparators and compared to the activity against *C. albicans* and *C. glabrata*.

Materials & methods

EUCAST AFST according to E.Def 7.3.1 was performed for ibrexafungerp. Methods in brief:

- 122 clinical *C. auris* isolates (from India (n=120) and Oman (n=2)) and three *C. auris* reference 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) prepared using the ISO method.
- Comparison of ibrexafungerp MICs to previously published MICs for anidulafungin, micafungin, amphotericin B, fluconazole, isavuconazole, itraconazole, posaconazole and voriconazole.

Results

C. auris

The *in vitro* activity of ibrexafungerp (IBX) against *C. auris* was uniform with MICs displaying a Gaussian distribution suggesting an equal efficacy across the 122 isolates (Table). The modal MIC and MIC_{50} were 0.5 mg/L. Ibrexafungerp MICs remained low for the isolates resistant to anidulafungin and micafungin (MICs >32 mg/L) (Figure 1).

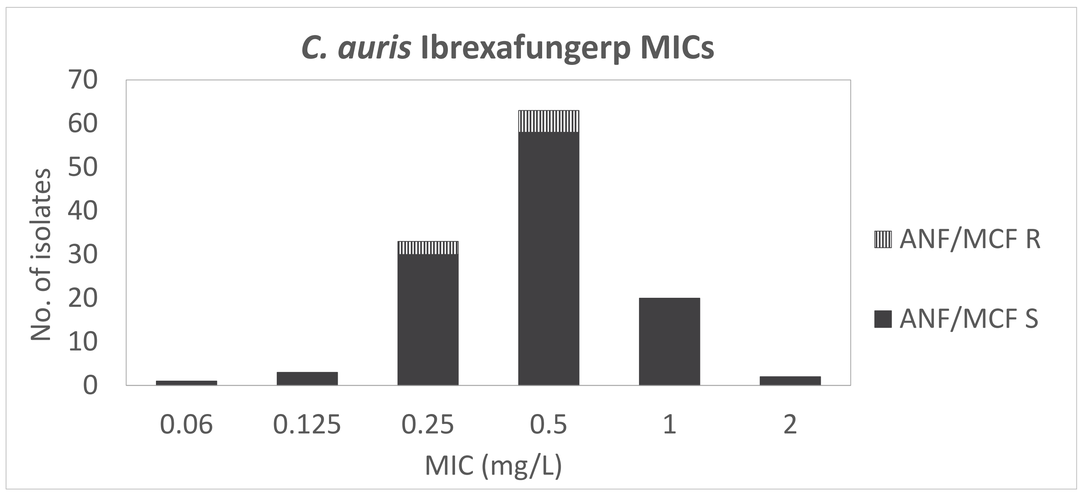

Figure 1. Ibrexafungerp MICs against the 122 clinical *C. auris* isolates.

Ibrexafungerp and comparators

MIC distributions for anidulafungin (ANF), micafungin (MCF), isavuconazole (ISA), voriconazole (VOR), itraconazole (ITR) and posaconazole (PRC) against *C. auris* were wide suggesting differential activity against the isolates. Fluconazole (FLU) MICs for all but one isolate were 16- >256 mg/L suggesting almost universal fluconazole resistance. The amphotericin B (AMB) MICs clustered close to the non-species specific breakpoint of 1 mg/L.

Comparison to *C. albicans* and *C. glabrata*

The activity of ibrexafungerp 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 (Figure 2).

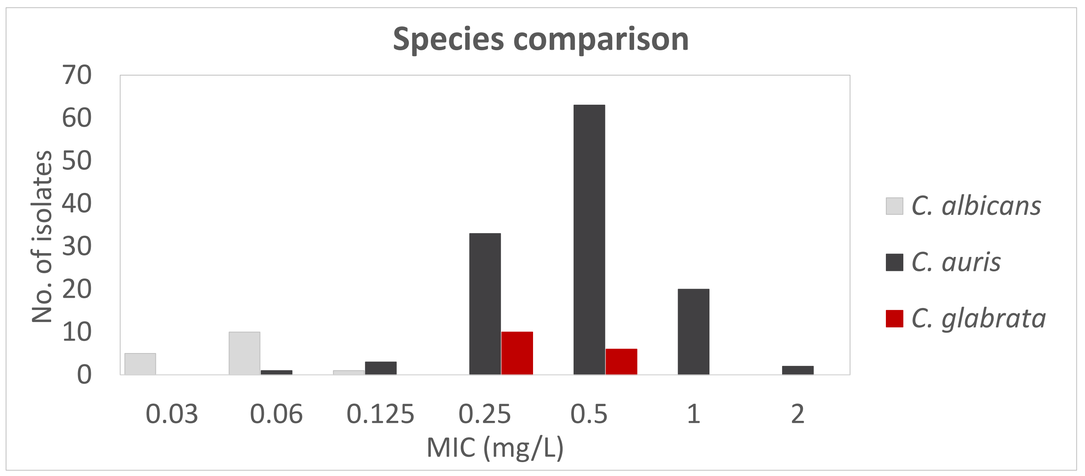

Figure 2. Comparison of ibrexafungerp MICs against clinical *C. auris* (n=122), *C. albicans* (n=16) and *C. glabrata* (n=16) isolates.

Reference and control strains

For the C. auris reference strains, JCM15448, KCTC17809 and KCTC17810, the MICs were 0.06 mg/L, 0.125 mg/L and 0.5 mg/L, respectively.

The MIC ranges for the nine repetitive MIC determinations of the control strains were:
C. albicans ATCC 64548: 0.06 mg/L
C. krusei ATCC 6258: 0.5-1 mg/L
C. parapsilosis ATCC 22019: 0.125-0.5 mg/L

Table. EUCAST 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										

Conclusion

- Ibrexafungerp shows promising *in vitro* activity against *C. auris* suggesting it may be a welcomed therapeutic against this emerging threat with few treatment options.
- Ibrexafungerp MICs were in general one step higher against *C. auris* than against *C. glabrata* and, notably, remained unchanged against *C. auris* isolates with antifungal resistance to the comparator drugs, including those highly echinocandin-resistant.

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