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EXPERIMENTAL THERAPEUTICS

In Vitro Activity of Ibrexafungerp (SCY-078) against *Candida auris* Isolates as Determined by EUCAST Methodology and Comparison with Activity against *C. albicans* and *C. glabrata* and with the Activities of Six Comparator Agents

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ABSTRACT Ibrexafungerp (SCY-078) is a novel first-in-class antifungal agent targeting glucan synthase. *Candida auris* is an emerging multidrug-resistant species that has caused outbreaks on five continents. We investigated the *in vitro* activity of ibrexafungerp against *C. auris* by applying EUCAST E.Def 7.3.1 methodology. *C. albicans* and *C. glabrata*, as well as anidulafungin, micafungin, amphotericin B, fluconazole, voriconazole, and isavuconazole, were included as comparators. Three *C. auris* reference strains (CBS12372, CBS12373, and CBS10913) and 122 *C. auris*, 16 *C. albicans*, and 16 *C. glabrata* isolates were evaluated. *C. albicans* ATCC 64548, *C. parapsilosis* ATCC 22019, and *C. krusei* ATCC 6258 served as quality control strains. Echinocandin-resistant isolates were *fks* sequenced. MIC ranges and modal MIC and MIC_{50} values were determined. Wild-type upper limits (the upper MIC value where the wild-type distribution ends) were determined according to EUCAST principles for setting ECOFFs. Nine repetitions of three QC strains and MICs for *C. albicans* and *C. glabrata* yielded narrow MIC ranges with modal MICs in agreement with established EUCAST modal MICs, confirming a robust test performance. The ibrexafungerp MICs against *C. auris* isolates displayed a Gaussian distribution with a modal MIC (range) of 0.5 mg/liter (0.06 to 2 mg/liter), suggesting uniform susceptibility. Of 122 isolates, 8 were echinocandin resistant and harbored the S639F Fks1 alteration. All but one were fluconazole resistant, and the MIC distributions for voriconazole and isavuconazole were multimodal confirming variable susceptibility. Ibrexafungerp demonstrated promising activity against *C. auris*, including isolates resistant to echinocandins and/or other agents. The MICs were similar to those reported for the Clinical and Laboratory Standards Institute method, suggesting that a common clinical breakpoint may be appropriate.

KEYWORDS ibrexafungerp, *C. auris*, antifungal susceptibility, echinocandin resistance, EUCAST, SCY078, antifungal susceptibility testing, *fks* mutation

Ibrexafungerp (formerly SCY-078) is a novel first-in-class antifungal agent with *in vitro* activity against yeast, molds, and pneumocystis. It is currently in two phase 2 open-label studies to evaluate its efficacy and safety in patients with candidiasis caused by *Candida auris* (CARES) and in patients with refractory or intolerant fungal diseases (FURI), respectively. In addition, a phase 3, multicenter, randomized, double-blind, placebo-controlled study is under way to evaluate the efficacy and safety in subjects with acute vulvovaginal candidiasis (VANISH). The drug target is glucan synthase, but

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TABLE 1 *In vitro* activity of ibrexafungerp and comparators against control isolates, as determined by EUCAST E.Def 7.3.1

EUCAST-recommended QC strains	No. of repetitions	MIC (mg/liter)							Range (mg/liter)	Tentative QC MIC target (range) in mg/liter
		0.03	0.06	0.125	0.25	0.5	1	2		
C. albicans ATCC 64548	9		9						0.06	0.06 (0.03–0.125)
C. krusei ATCC 6258	9					8	1		0.5–1	0.5 (0.25–1)
C. parapsilosis ATCC 22019	9			3	5	1			0.125–0.5	0.25 (0.125–0.5)
C. auris										
CBS10913	1		1							
CBS12372	1			1						
CBS12373	1					1				

unlike the echinocandins ibrexafungerp is administered orally and retains activity against some *fks* mutant *Candida* species isolates (1–4).

C. auris is a recently recognized emerging yeast species associated with outbreaks in health care settings (5). It is considered a major threat to intensive care unit patients with a reported crude in-hospital mortality rate ranging between 30 and 72% (6–9). Knowledge of antifungal susceptibility of *C. auris* is of primary concern since *C. auris* almost consistently exhibits high fluconazole MICs (except in Colombian isolates [10]) and variable susceptibility to the other azoles, echinocandins and amphotericin B. Thus, treatment options in patients with invasive disease due to *C. auris* may become limited. A recent study from the Centers for Disease Control and Prevention (Atlanta, GA) reported that 93% of investigated *C. auris* isolates were resistant to fluconazole, 35% were resistant to amphotericin B, and 7% were resistant to echinocandins when susceptibility tested according to Clinical and Laboratory Standards Institute (CLSI) methodology (11). New antifungal agents, including ibrexafungerp, fosmanogepix, and VT-1578, have displayed *in vitro* activity against *C. auris* (1, 12–15). Although the *in vitro* activity of ibrexafungerp against *C. auris* has been investigated by the CLSI method M27-A3, MIC data obtained using the EUCAST methodology are scarce (16). Because MICs may differ among different susceptibility tests, the objective of the present study was to evaluate the *in vitro* activity of ibrexafungerp by the EUCAST E.Def 7.3.1 reference microdilution method. A large panel of well-identified nonduplicate clinical *C. auris* isolates, including both highly fluconazole- and echinocandin-resistant isolates and those in the susceptible range, were included, and the *in vitro* activity was compared to that of six comparator antifungal agents and to that against *C. albicans* and *C. glabrata*.

RESULTS

Nine repetitive tests of three recommended AFST quality control (QC) strains (*C. albicans* ATCC 64548, *C. krusei* ATCC 6258, and *C. parapsilosis* ATCC 22019) generated MICs that fell within one to three dilutions, suggesting a robust susceptibility test performance. The modal MICs were as follows: *C. albicans* ATCC 64548, 0.06 mg/liter; *C. krusei* ATCC 6258, 0.5 mg/liter; and *C. parapsilosis* ATCC 22019, 0.25 mg/liter (Table 1).

The EUCAST MICs of ibrexafungerp against the 122 *C. auris* isolates displayed a Gaussian distribution with a modal MIC and an MIC_{50} of 0.5 mg/liter and a range of 0.06 to 2 mg/liter (Table 2). The wild-type upper limit was 1 mg/liter determined visually, as well as by using the ECOFFinder program with 95, 97.5, or 99% of the modeled population included. The statistically fitted wild-type MIC curve was almost identical to the raw MIC curve (Fig. 1), confirming a robust susceptibility testing method and a population without isolates with acquired resistance mechanisms to ibrexafungerp. The MIC ranges for anidulafungin and micafungin were notably wider (0.016 to >32 mg/liter and 0.03 to >32 mg/liter, respectively) with eight isolates displaying high MICs (anidulafungin [4 to 32 mg/liter] and micafungin [32 mg/liter]) (Table 2). These isolates harbored the following *fks* alterations: S639F ($n = 8$) and all displayed wild-type susceptibility to ibrexafungerp (MICs of 0.25 mg/liter ($n = 3$) or 0.5 mg/liter ($n = 5$). All but one *C. auris* isolates were highly fluconazole resistant, and the MIC distributions for

TABLE 2 *In vitro* activity of ibrexafungerp (IBX) and comparators against *C. auris* and selected *C. albicans* and *C. glabrata* isolates, as determined by EUCAST E.Def 7.3.1[a]

Strain and agent	MIC (mg/liter)															MIC range (mg/liter)	Modal MIC (mg/liter)	MIC_{50} (mg/liter)
	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	≥64			
C. auris (n = 122)																		
IBX					1	3	33	63	20	2						0.06–2	0.5	0.5
ANF*			1	11	35	30	12	12	11	2	1			7		0.016–>32	0.06	0.125
MCF*				5	30	70	9							8		0.03–>32	0.125	0.125
AMB*								14	108							0.5–1	1	1
FLU*								1					2	10	109	0.5–≥64	≥64	≥64
VOR*	1			1	1	16	13	34	38	13	5					≤0.004–4	Bimodal	0.5
ISA*	20	1	1	19	9	19	21	21	6	5						≤0.004–2	Trimodal	0.125
C. albicans (n = 16)																		
IBX				5	10	1										0.03–0.125	0.06	0.06
ANF	10	6														≤0.004–0.008	≤0.004	≤0.004
MCF		4	10	2												0.008–0.03	0.016	0.016
AMB					1	6	9									0.06–0.25	0.25	0.25
FLU						10	6									0.125–0.25	0.125	0.125
VOR	12	4														≤0.004–0.008	≤0.004	≤0.004
ISA	14	2														≤0.004–0.008	≤0.004	≤0.004
C. glabrata (n = 16)																		
IBX							10	6								0.25–0.5	0.25	0.25
ANF			4	12												0.016–0.03	0.03	0.03
MCF			8	8												0.016-0.03	0.016/0.03	0.016
AMB				1		1	11	3								0.03–0.5	0.25	0.25
FLU										6	10					2–4	4	4
VOR				1	13	2										0.03–0.125	0.06	0.06
ISA			1	3	6	6										0.016–0.125	0.06/0.125	0.06

[a]Gray-shaded areas indicate concentrations not tested for that particular compound. An underlined value indicates a modal MIC for unimodal distributions but the lowest MIC peak for multimodal distributions, thus illustrating the modal MIC of the presumed wild-type distribution. The MIC distributions for comparator antifungals against *C. auris* indicated by an asterisk (*) are compiled from reference 1 except that isolates above the tested MIC range in that publication were retested using extended concentration ranges.

voriconazole and posaconazole were bi- and trimodal, suggesting variable susceptibility to these azoles. Finally, all isolates would be categorized as amphotericin B susceptible if adopting the breakpoint of 1 mg/liter; however, the MICs of 108/122 (88.5%) of the isolates fell at 1 mg/liter which are three, two, and one dilution greater than the

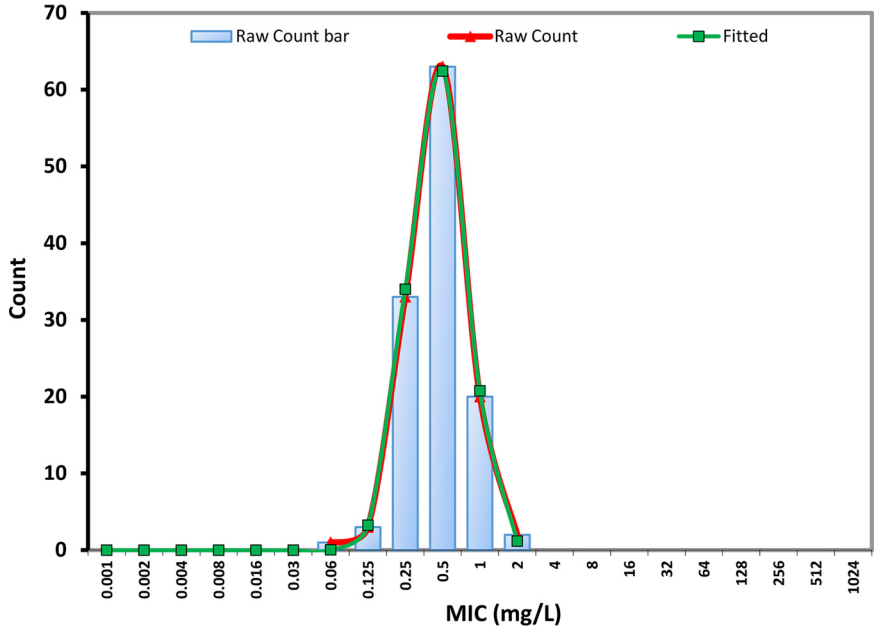

FIG 1 EUCAST MIC distribution for ibrexafungerp against 122 clinical *C. auris* isolates. Raw counts are presented as bars and a red curve, whereas the fitted curve was determined by the ECOFF finder program (v2.0) that iteratively fits each subset of the data from left to right.

EUCAST amphotericin B modal MIC for *C. albicans*, *C. glabrata*, and *C. krusei*, respectively (17). Thus, on a mg/liter basis ibrexafungerp was more active than amphotericin B and fluconazole and less active than the other four comparators when tested by EUCAST.

Finally, the ibrexafungerp MICs were determined for 16 *C. albicans* and 16 *C. glabrata* isolates (Table 2). The MIC ranges were narrow spanning three and two 2-fold dilutions, respectively, again suggesting a robust test performance, with modal MICs of 0.06 mg/liter (as for the repetitive testing of the *C. albicans* QC strain) and 0.25 mg/liter, respectively. The modal MICs for the comparator compounds were in agreement within ± one 2-fold dilution of the aggregated MIC data used for EUCAST breakpoint setting (EUCAST modal MICs for *C. albicans*/*C. glabrata* as follows: anidulafungin, 0.004/0.016; micafungin, 0.008/0.008; amphotericin B, 0.125/0.25; fluconazole, 0.25/8; and voriconazole, 0.008/0.125 mg/liter), again suggesting a robust performance of the susceptibility testing in this study (18).

DISCUSSION

Ibrexafungerp displayed uniform and potent activity against the 122 *C. auris* strains, including 8 that were anidulafungin and micafungin resistant. Activity against echinocandin-resistant *C. auris* isolates has previously been reported when tested by the CLSI method, though without information regarding the underlying molecular resistance mechanisms (1). Moreover, it has been demonstrated that ibrexafungerp retains activity against some *fks* mutants of *C. glabrata* (2–4, 19) and against a limited number of *fks* mutants of *C. albicans*, *C. dubliniensis*, *C. tropicalis*, and *C. krusei* isolates (4). *C. auris* is phylogenetically related to *C. glabrata*. The ibrexafungerp *in vitro* activity was recently investigated against 79 *C. glabrata* harboring 29 different hot spots alterations recognized to cause MIC elevations for the echinocandins. Elevated ibrexafungerp MICs were found against *C. glabrata* isolates with 3 out of 11 investigated fks1 alterations (625S, D632G, and D632Y) and against 5 of 18 fks2 alterations (F659del, F659S, F659V, L662W, and S663P) (20). Of note, ibrexafungerp MICs were not elevated against four included isolates harboring the S663F alteration in Fks2, which corresponds to the S639F alteration found in Fks1 of the eight highly echinocandin-resistant *C. auris* isolates included in this study.

The modal MIC obtained by EUCAST against *C. auris* was equal to or one 2-fold dilution lower than the modal MIC values previously obtained by the CLSI methodology (1, 12). Similarly, the modal MIC against *C. albicans* and *C. glabrata* were identical to those obtained by Marcos-Zambrano et al. using EUCAST and to those obtained by Schell et al. using CLSI and finally one step lower and one step higher, respectively, than those obtained by Pfaller et al. and Marcos-Zambrano et al. using CLSI methods (2, 4, 16). Taken together, these data suggest an excellent agreement between EUCAST and CLSI testing for *C. auris*, *C. albicans*, and *C. glabrata*, which may allow a single species-specific clinical breakpoint to be set for each of the organisms that will apply for both EUCAST and CLSI testing. This has obvious advantages. The EUCAST and CLSI MICs for anidulafungin and micafungin were not comparable, and as a result method-specific clinical breakpoints have been established (for example, the EUCAST susceptibility breakpoint is 0.03 mg/liter for *C. albicans* compared to 0.25 mg/liter for CLSI). Such method disagreement complicates MIC interpretation and the development of commercial susceptibility tests that correctly categorizes isolates as susceptible or resistant according to both standards.

In summary, our data confirm that ibrexafungerp appears to be a promising future agent against *C. auris* infections, including those involving acquired echinocandin or azole resistance. We demonstrate that EUCAST MIC testing of ibrexafungerp is robust against *C. auris*, as well as *C. albicans* and *C. glabrata*, and that EUCAST MICs mirror those obtained by CLSI testing, suggesting that mutual breakpoints for the two methods can be established. In light of the multiple-drug-resistant and highly transmissible potential for *C. auris*, these findings are a welcome step forward. Nevertheless, further studies, including studies of *C. auris* isolates from other parts of the world, are

warranted, since differential susceptibilities to licensed compounds have been found among different *C. auris* clades.

MATERIALS AND METHODS

Isolates. Three control *C. auris* strains (CBS12372, CBS12373, and CBS10913) and a total of 122 clinical isolates of *C. auris* collected from individual patients in six tertiary care hospitals in India from 2010 to 2015 were included. The clinical isolates were mainly from patients with candidemia (blood; $n = 100$), and other specimens ($n = 22$) from invasive *Candida* infections included tissue, pleural fluid, and a single isolate from pus. Species identification was performed using sequencing of the internal transcribed spacer region of the ribosomal subunit and confirmed by using a Bruker MALDI TOF MS apparatus before use. Eight were anidulafungin and echinocandin resistant and were *fks* sequenced as previously described (21). To confirm assay performance, an additional 16 drug-susceptible clinical isolates of *C. albicans* and *C. glabrata* from Danish patients were included. Finally, nine repetitions for the CLSI and EUCAST QC strains *C. albicans* ATCC 64548, *C. parapsilosis* ATCC 22019, and *C. krusei* ATCC 6258 were performed.

Susceptibility testing. EUCAST MICs were determined following E.Def 7.3.1 methodology (22). Ibrexafungerp (SCY-078; Scynexis, Inc., Jersey City, NJ) pure substance was stored in aliquots at −80°C, and stock solutions were prepared in dimethyl sulfoxide (5,000 mg/liter; Sigma-Aldrich, Brøndby, Denmark). The final drug concentration ranges studied were 0.008 to 4 mg/liter. The following comparator compounds were also investigated (source of compound with the final concentration ranges in parentheses): anidulafungin (Pfizer A/S, Ballerup, Denmark; 0.004 to 4 mg/liter for *C. albicans* and *C. glabrata* isolates and 0.03 to 32 mg/liter for *C. auris*), micafungin (Astellas Pharma, Inc., Tokyo, Japan; 0.004 to 4 mg/liter for *C. albicans* and *C. glabrata* isolates and 0.03 to 32 mg/liter for *C. auris*), amphotericin B (Sigma-Aldrich; 0.004 to 4 mg/liter), fluconazole (Sigma-Aldrich; 0.03 to 32 mg/liter for bloodstream isolates and 0.5 to 256 mg/liter for *C. auris*), isavuconazole (Basilea Pharmaceutica, Ltd., Basel, Switzerland; 0.004 to 4 mg/liter), and voriconazole (Pfizer A/S, Ballerup, Denmark; 0.004 to 4 mg/liter) (23). Cell culture-treated samples (Nunc MicroWell 96-well microplates; Thermo Fisher Scientific, catalog no. 167008) were used throughout. Microtiter plates with 2-fold dilutions were prepared and frozen at −80°C prior to use.

Data management. MIC ranges, modal MIC (the most common MIC), and MIC_{50} (i.e., the MIC that includes 50% of the isolates) values were calculated. Wild-type upper limits (WT-ULs), defined as the upper MIC value where the wild-type distribution ends, were determined following principles for setting EUCAST ECOFFs. However, since the values reported here are not formally accepted EUCAST ibrexafungerp ECOFFs, we use the term "WT-UL" to avoid confusion. The conventional method for determining an ECOFF is a visual inspection of histograms of the MICs for single species ("the eyeball method") (24). In addition, WT-ULs were determined statistically using the EUCAST ECOFFinder program (24).

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