**In Vitro Antifungal Activity of Ibrexafungerp (SCY-078) Against Contemporary Blood Isolates From Medically Relevant Species of Candida: A European Study**

Guillermo Quindós*,†§, Katherine Miranda-Cadena**, Rosario San-Millán**,†§, Katyna Borroto-Esoda**, Emilia Cantón**, María José Linares-Sicilia**, Axel Hamprecht**, Isabel Montesinos**, Anna Maria Tortorano**, Anna Prigiano**, Maxalet Vidal-García***, Cristina Marcos-Arias**, Andrea Guridi**, Ferran Sanchez-Reus**, Jesús Machuca-Bárceña**, Manuel Antonio Rodriguez-Iglesias**, Estrella Martín-Mazuelos**, Carmen Castro-Méndez**, Leyre López-Soria**, Alba Ruiz-Gaitán**, Marcelo Fernandez-Rivero**, Damaris Lorenzo**, Javier Capilla**,‡ Antonio Rezusta**, Javier Pemán**, Josep Guarro**, Joana Pereira**, Célia Pais**, Orazio Romeo**, Guillermo Ezeleta**, Nerea Jauregizar**, David Angulo** and Elena Eraso**

Background: Ibrexafungerp (SCY-078) is the newest oral and intravenous antifungal drug with broad activity, currently undergoing clinical trials for invasive candidiasis.

Objective: The aim of this study was to assess the in vitro activity of ibrexafungerp and comparators against a collection of 434 European blood isolates of Candida.

Methods: Ibrexafungerp, caspofungin, fluconazole, and micafungin minimum inhibitory concentrations (MICs) were collected from 12 European laboratories for 434 blood isolates, including 163 Candida albicans, 108 Candida parapsilosis, 60 Candida glabrata, 40 Candida tropicalis, 29 Candida krusei, 20 Candida orthopsilosis, 6 Candida guilliermondii, 2 Candida famata, 2 Candida lusitaniae, and 1 isolate each of...
INTRODUCTION

Invasive candidiasis (IC) is the most common healthcare-associated invasive mycosis, being a major cause of human morbidity and mortality. Candida albicans is the most prevalent etiology, but other species, such as Candida glabrata, Candida parapsilosis, Candida krusei (Pichia kudriavzevii), and, more recently, Candida auris, are increasing causes of IC. These emergent species are usually less susceptible to current antifungal drugs. Although Candida isolates displaying antifungal resistance are still uncommon, they are increasingly reported worldwide. Therapy of IC is an unsolved clinical challenge and, for this reason, monitoring antifungal susceptibility patterns and resistance mechanisms is of utmost importance. Moreover, new antifungal drugs are needed as the number of available antifungal drug classes, and particularly those for oral administration, is limited (Arendrup and Patterson, 2017; Quindós et al., 2018; Fuller et al., 2019; Pfaller et al., 2019).

Ibrexafungerp (formerly SCY-078) is a semisynthetic triterpenoid glycoside derived from enfumafungin, which is structurally different from echinocandins and form a new class of antifungal drugs called “fungers” that strongly inhibit fungal 1,3-β-glucan synthase (Davis et al., 2020). Even ibrexafungerp and echinocandins share similar mechanisms of action, and their binding sites to the target enzyme is not the same, resulting in very limited cross-resistance (Jiménez-Ortigosa et al., 2017; Pfaller et al., 2017). Ibrexafungerp displays significant in vitro and in vivo activities against azole- and echinocandin-resistant isolates of Candida species, including biofilm-forming strains (Jiménez-Ortigosa et al., 2014; Pfaller et al., 2017; Schell et al., 2017; Gamal et al., 2021).

Ibrexafungerp aims to be the first orally and intravenously available glucan synthase inhibitor useful in the treatment of life-threatening fungal infections (Davis et al., 2020) as well as superficial ones, such as vulvovaginal candidiasis (Schwebke et al., 2021; Sobel et al., 2022). Currently, there are 13 listed clinical trials for ibrexafungerp, eight of which have been completed (https://ClinicalTrials.gov/; accessed on March 8, 2022).

In the current study, we have determined the anti-Candida in vitro activity of ibrexafungerp, caspofungin, fluconazole, and micafungin against 434 European Candida blood isolates analyzed in 12 European laboratories.

RESULTS

Ibrexafungerp MICs ranged from 0.016 to ≥8 mg/L. The lowest ibrexafungerp MICs were observed for C. albicans (geometric MIC 0.062 mg/L, MIC range 0.016–0.5 mg/L) and the highest ibrexafungerp MICs were observed for C. tropicalis (geometric MIC 0.517 mg/L, MIC range 0.06–≥8 mg/L). Modal MICs/MIC₅₀S (mg/L) against Candida spp. were 0.125/0.06 for C. albicans, 0.5/0.5 for C. parapsilosis, 0.25/0.25 for C. glabrata, 0.5/0.5 for C. tropicalis, 1/1 for C. krusei, 4/2 for C. orthopsilosis, and 0.5/0.5 for C. auris. Ibrexafungerp showed activity against fluconazole- and echinocandin-resistant isolates. If adopting wild-type upper limits, a non-wild-type phenotype for ibrexafungerp was only observed for 16/434 (3.7%) isolates: 11 (4.6%) C. parapsilosis, 4 (5%) C. glabrata, and 1 (2.5%) C. tropicalis.

Conclusion: Ibrexafungerp showed a potent in vitro activity against Candida.

Keywords: antifungal testing, antifungal resistance, Candida, ibrexafungerp, SCY-078, EUCAST, caspofungin, micafungin

MATERIALS AND METHODS

Microorganisms

In vitro susceptibility of a collection of 434 Candida blood isolates (2016–2018) from 434 patients was determined at 12 laboratories from Belgium, Germany, Italy, Portugal, and Spain.
Each laboratory studied its own clinical isolates. The collection included 163 *C. albicans*, 108 *C. parapsilosis*, 60 *C. glabrata*, 40 *C. tropicalis*, 29 *C. krusei*, 20 *Candida orthopsilosis*, 6 *Candida guilliermondii* (Meyerozyma guilliermondii), 2 *Candida famata* (Debaryomyces hansenii), 2 *Candida lusitaniae* (Clavispora lusitaniae), and 1 isolate each of *Candida bracarensis, Candida catenulata* (Diutina catenulata), *Candida dubliniensis*, and *Candida kefyr* (Kluyveromyces marxianus). Additionally, 22 *C. auris* from different clinical specimens were evaluated: Eight isolates were from blood, seven from oral specimens, and 7 from urine (Ruiz-Gaita et al., 2017; Ruiz-Gaita et al., 2018). Isolates were identified by phenotypic methods, MALDI-TOF (proteomic method), and, when needed, internal transcribed spacer (ITS) sequencing (genotypic method) (Miranda-Zapico et al., 2011). *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were included as quality control (QC) strains. Reference strain *C. albicans* ATCC 64550 was also included as recommended by EUCAST for detecting variation in strain pharmacodynamics (PK/PD) parameters should be taken into account. The study was approved by the Ethics Committee of the Universidad del Pais Vasco/Euskal Herriko Unibertsitatea (UPV/EHU, Bilbao, Spain, CEIAB Ethics reference number M30_2015_248).

**RESULTS**

MICs of ibrexafungerp against all species were tested *in vitro* ranging from 0.016 to ≥8 mg/L (*MIC* ≤ 2 mg/L). These values were comparable to those of caspofungin and micafungin (*MIC* ≤ 2 mg/L). The lowest ibrexafungerp MICs were observed for *C. albicans* (GM 0.062 mg/L, MM range 0.016–0.5 mg/L, *MIC* ≤ 0.125 mg/L) and the highest ibrexafungerp MICs were observed for *C. tropicalis* (GM 0.517 mg/L, MM range 0.06–8 mg/L, *MIC* 2 mg/L) (*Table 1*). Echinocandins MIC values for *C. albicans* ranged from ≤ 0.008 mg/L to ≥2 mg/L for micafungin (MM 0.008 mg/L, GM 0.001 mg/L, *MIC* 0.016 mg/L) and from 0.016 mg/L to ≥2 mg/L for caspofungin (MM 0.125 mg/L, GM 0.104 mg/L, *MIC* 0.125 mg/L). For the three isolates with elevated caspofungin or micafungin MICs, ibrexafungerp MIC range was 0.06 mg/L to 0.25 mg/L. In the current report, ibrexafungerp MICs ranged from 0.016 mg/L to ≥8 mg/L for 108 *C. parapsilosis* isolates (MM 0.5 mg/L, GM 0.660 mg/L, *MIC* 4 mg/L) (*Table 2*). If we consider ibrexafungerp WTULs (>2 mg/L) obtained in this study, 11 *C. parapsilosis* isolates were NWT (4.6%). These NWT isolates were inhibited by ≤1 mg/L of fluconazole and by ≤4 mg/L of caspofungin or micafungin. We also observed that for six *C. parapsilosis* NWT (5.6%) and two resistant isolates to fluconazole (0.9%), the MIC range of ibrexafungerp was 0.5–2 mg/L. According to MIC90s, ibrexafungerp showed comparable values with caspofungin (MM 1 mg/L, GM 0.846 mg/L, *MIC* 2 mg/L) and micafungin (MM 2 mg/L, GM 0.933 mg/L, *MIC* 2 mg/L). Moreover, two isolates resistant to micafungin were inhibited by 2 mg/L of ibrexafungerp.

Ibrexafungerp also displayed potent *in vitro* activity against 60 *C. glabrata* isolates (*MIC* range 0.016–8 mg/L, MM 0.25 mg/L, GM 0.322 mg/L, *MIC* 1 mg/L) (*Table 2*). Sixteen *C. glabrata* isolates resistant to fluconazole were inhibited by ≤1 mg/L of ibrexafungerp. Among 9 *C. glabrata* isolates with elevated MICs to caspofungin or/and micafungin, the MIC range for...
Ibrexafungerp was 0.25 mg/L to 4 mg/L with a MIC_{50} of 1 mg/L. It was notable that whereas the increase in MM between C. glabrata WT and NWT isolates was 4-fold for caspofungin and 63-fold for micafungin, MM values for ibrexafungerp did not increase (Table 3).

In vitro activity of ibrexafungerp was also observed against 40 C. tropicalis blood isolates and MICs ranged from 0.06 mg/L to ≥8 mg/L (MM 0.5 mg/L, GM 0.517 mg/L, MIC_{90} 2 mg/L) (Table 2). Against 14 C. tropicalis resistant to fluconazole, ibrexafungerp MIC range was 0.25–2 mg/L (MIC_{90} 1 mg/L).

Moreover, ibrexafungerp showed high in vitro activity against 29 C. krusei (MIC range 0.125–1 mg/L, MM 1 mg/L, GM 0.666 mg/L, MIC_{90} were 1 mg/L). MIC values of micafungin ranged from 0.03 mg/L to 0.25 mg/L (MM 0.125 mg/L, GM 0.122 mg/L, MIC_{90} 0.125 mg/L) and from 0.25 mg/L to 1 mg/L for caspofungin (MM 0.5 mg/L, GM 0.465 mg/L, MIC_{90} 1 mg/L). Additionally, all C. auris isolates were resistant in vitro to fluconazole (MIC ≥ 128 mg/L) while ibrexafungerp showed activity (MIC range 0.5 mg/L to 8 mg/L, MM 0.5 mg/L, GM 0.753 mg/L, MIC_{90} 2 mg/L) (Table 4). C. auris urinary isolates showed higher MICs (data not shown). Against this species, the activity of ibrexafungerp was similar to the activity of micafungin (MIC range 0.125–8 mg/L, MM 0.125 mg/L, GM 0.377 mg/L, MIC_{90} 4 mg/L) and 8-fold more active than caspofungin (MIC range 0.25–8 mg/L, MM 0.25 mg/L, GM 0.465 mg/L, MIC_{90} >8 mg/L). Among six isolates with elevated caspofungin or/and micafungin MICs, ibrexafungerp MICs ranged from 0.5 mg/L to 8 mg/L (MIC_{50} 0.5 mg/L).

MICs of ibrexafungerp were ≤1 mg/L for the 2 C. famata isolates and 1 isolate each of C. catenulata, C. dubliniensis, and C. kefyr (Table 5). Ibrexafungerp MIC_{50} was 2 mg/L for the 6 C. guilliermondii blood isolates with a MIC range from 2 to 4 mg/L, being twofold less active than caspofungin or micafungin.

**DISCUSSION**

The present study aimed to evaluate the in vitro activity of ibrexafungerp against a collection of 434 European blood isolates.
| Species/Antifungal drugs | ≤0.008 | 0.016 | 0.03 | 0.06 | 0.0125 | 0.025 | 0.05 | 0.1 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | ≥128 |
|--------------------------|--------|-------|------|------|--------|-------|------|-----|------|-----|----|---|---|---|---|----|----|----|-----|
|                          | Range  | Mode  | GM  | 50   | 90     |       |      |     |      |     |    |   |   |   |   |    |
| Candida albicans (n = 163) |        |       |     |      |        |       |      |     |      |     |    |   |   |   |   |    |
| Ibrexafungerp            | 0      | 2     | 48  | 50  | 0      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Caspofungin              | 0      | 0     | 3   | 1   | 2      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Micafungin               | 82     | 79    | 1   | 0   | 0      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Fluconazole              | -      | 0     | 1   | 0   | 0      | 0     | 0    | 0   | 0    | 0   | 1 | 0 | 0 | 0 | 0 | 1  |
| Candida parapsilosis (n = 108) |        |       |     |      |        |       |      |     |      |     |    |   |   |   |   |    |
| Ibrexafungerp            | 0      | 6     | 5   | 1   | 4      | 0     | 2    | 1   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Caspofungin              | 0      | 0     | 0   | 0   | 0      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Micafungin               | 3      | 3     | 3   | 2   | 4      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Fluconazole              | -      | -     | -   | -   | -      | -     | -    | -   | -    | -   | -  | - | - | - | - | -  |
| Candida glabrata (n = 60) |        |       |     |      |        |       |      |     |      |     |    |   |   |   |   |    |
| Ibrexafungerp            | 0      | 2     | 3   | 0   | 1      | 1     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Caspofungin              | 0      | 0     | 0   | 0   | 3      | 28    | 1    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Micafungin               | 18     | 30    | 3   | 0   | 0      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Fluconazole              | -      | -     | -   | -   | -      | -     | -    | -   | -    | -   | -  | - | - | - | - | -  |
| Candida tropicalis (n = 40) |        |       |     |      |        |       |      |     |      |     |    |   |   |   |   |    |
| Ibrexafungerp            | 0      | 0     | 0   | 0   | 0      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Caspofungin              | 0      | 0     | 0   | 0   | 0      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Micafungin               | 1      | 2     | 5   | 0   | 0      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Fluconazole              | -      | -     | -   | -   | -      | -     | -    | -   | -    | -   | -  | - | - | - | - | -  |
| Candida krusei (n = 29)  |        |       |     |      |        |       |      |     |      |     |    |   |   |   |   |    |
| Ibrexafungerp            | 0      | 0     | 0   | 0   | 0      | 1     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Caspofungin              | 0      | 0     | 0   | 0   | 0      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Micafungin               | 0      | 1     | 3   | 1   | 2      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Fluconazole              | -      | -     | -   | -   | -      | -     | -    | -   | -    | -   | -  | - | - | - | - | -  |
| Candida orthopsilosis (n = 20) |        |       |     |      |        |       |      |     |      |     |    |   |   |   |   |    |
| Ibrexafungerp            | 0      | 0     | 0   | 0   | 0      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Caspofungin              | 0      | 0     | 0   | 0   | 0      | 0     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Micafungin               | 0      | 0     | 1   | 3   | 1      | 4     | 0    | 0   | 0    | 0   | 0  | 0 | 0 | 0 | 0 | 0  |
| Fluconazole              | -      | -     | -   | -   | -      | -     | -    | -   | -    | -   | -  | - | - | - | - | -  |

(Continued)
of Candida. Ibrexafungerp showed a potent in vitro activity against Candida, with MICs ranging from 0.016 to 16 mg/L. The lowest ibrexafungerp MICs were observed against C. albicans and the highest ibrexafungerp MICs were observed against C. tropicalis. Moreover, ibrexafungerp also displayed remarkable activity against fluconazole- and echinocandin-resistant isolates.

Five species of Candida (C. albicans, C. parapsilosis, C. glabrata, C. tropicalis, and C. krusei) cause more than 90% of IC (Quindós et al., 2014; Arendrup and Patterson, 2017; Quindós et al., 2018). C. albicans remains the predominant cause, but there is an evident shift in the etiology, and IC caused by other species less susceptible to current antifungal drugs is becoming more frequent (Fuller et al., 2019; Pfaffer et al., 2019). Echinocandins, such as anidulafungin, caspofungin, and micafungin, are considered first-line therapy for IC because they possess fungicidal activity against Candida (Gil-Alonso et al., 2015a; Gil-Alonso et al., 2015b). However, emergence of azole- and echinocandin-resistant [multidrug-resistant (MDR)] isolates has been reported for C. auris, C. glabrata, C. guilliermondii, C. lusitaniae, and C. parapsilosis (Lortholary et al., 2011; Pernán et al., 2012; Pfaffer et al., 2012; Alexander et al., 2013; Pham et al., 2014; Dudiuk et al., 2017; Ruiz-Gaitán et al., 2019; Tortorano et al., 2021). MDR Candida isolates complicate clinical decision-making and are associated with treatment failure and high mortality rates (Lortholary et al., 2011; Alexander et al., 2013; Shields et al., 2013; Quindós et al., 2018; Tortorano et al., 2021).

Ibrexafungerp is a novel orally bioavailable semi-synthetic derivative of the terpenoid enfumafungin that inhibits glucan synthase, decreasing 1,3-β-D-glucan polymers and weakening fungal cell wall (Jiménez-Ortigosa et al., 2014; Pfaffer et al., 2017; Schell et al., 2017; Davis et al., 2020). The current study that has evaluated European blood isolates confirms and extends the observations published in previous studies (Pfaffer et al., 2013; Jiménez-Ortigosa et al., 2014; Berkow et al., 2017; Larkin et al., 2017; Marcos-Zambrano et al., 2017; Pfaffer et al., 2017; Schell et al., 2017; Nunnally et al., 2019; Gamal et al., 2021). However, these previous studies have mostly tested American isolates. Our study with European isolates is in line with the conclusion that ibrexafungerp displays potent in vitro activity against the most clinically relevant species of Candida.

Ibrexafungerp showed an excellent activity against the C. albicans isolates included in the present study (MIC range 0.016–0.5 mg/L). These results confirm previous findings by other authors, such as Jiménez-Ortigosa et al. (2014); Schell et al. (2017), and Mesquida et al. (2021), demonstrating that ibrexafungerp showed activity against most FKS-mediated echinocandin-resistant C. albicans and against azole-resistant C. albicans.

Although there are no clinical breakpoints (CBPs) or ECVs available for ibrexafungerp, the study by Mesquida et al. (2022) as well as the present work have proposed WTULs. There are no differences in the proposed limits for C. glabrata (1 mg/L). However, our study suggests higher WTUL for C. albicans (0.5 mg/L vs. 0.25 mg/L by Mesquida et al.), for C. parapsilosis and C. tropicalis (2 mg/L vs. 1 mg/L by Mesquida et al.), and for C. krusei (4 mg/L vs. 2 mg/L by Mesquida et al.).
**TABLE 3** | MICs distribution of ibrexafungerp and comparator antifungal drugs against echinocandin wild-type (WT) and non-wild-type/resistant (NWTR) Candida spp. isolates.

| Species                  | Phenotype (no. of isolates) | Modal MIC (MIC range) [mg/L] |
|--------------------------|-----------------------------|-------------------------------|
|                          | Ibrexafungerp               | Caspofungin                   | Micafungin                    | Fluconazole                   |
| *Candida albicans*       | WT (160)                    | 0.125 (0.016–2)               | 0.125 (0.016–0.5)             | 0.016 (0.008–0.016)           | 0.25 (0.125–128)               |
|                          | NWTR (3)                    | ≤0.03 (0.03–0.25)             | ≤0.125 (≤0.125–2)             | ≤0.03 (≤0.03–8)               | 0.25 (0.25)                    |
| *Candida parapsilosis*   | WT (106)                    | 0.5 (0.06–8)                  | 1 (0.06–4)                    | 2 (≤0.008–2)                  | 0.25 (0.25–128)                |
|                          | NWTR (2)                    | 2 (2)                         | 1 (1–2)                       | 4 (4)                        | ≤0.25 (≤0.25–4)                |
| *Candida glabrata*       | WT (61)                     | 0.25 (0.016–8)                | 0.25 (0.06–0.5)               | 0.016 (≤0.008–0.03)          | 8 (0.25–≥128)                  |
|                          | NWTR (9)                    | 0.25 (0.25–4)                 | 1 (0.5–≥8)                    | 1 (0.06–2)                   | 128 (0.5–128)                  |
| *Candida tropicalis*     | WT (59)                     | 0.25 (0.03–8)                 | 0.25 (0.03–8)                 | 0.5 (0.03–8)                 | 0.25 (0.03–16)                 |
|                          | NWTR (1)                    | ≥8 (>8)                       | ≥8 (>8)                       | 0.5 (0.5)                    | 0.25 (0.25)                    |
| *Candida orthopsilosis*  | WT (16)                     | 4 (0.06–4)                    | 2 (0.25–2)                    | 1 (0.06–2)                   | 0.5 (0.125–16)                 |
|                          | NWTR (4)                    | 4 (2–4)                       | 4 (4)                         | 1 (1–2)                      | 0.5 (0.5–1)                    |
| *Candida auris*          | WT (16)                     | 0.5 (0.5–4)                   | 0.25 (0.25–2)                 | 0.25 (0.25–1)                | ≥128 (≥128)                    |
|                          | NWTR (6)                    | 0.5 (0.5–8)                   | >8 (≥8)                       | 1 (1–8)                      | ≥128 (≥128)                    |
| *Candida guilliermondii* | WT (5)                      | 2 (2–4)                       | 0.5 (0.5–1)                   | 0.5 (0.5–1)                  | 0.5 (0.5–64)                   |
|                          | NWTR (1)                    | 4 (4)                         | 8 (8)                         | 0.008 (0.008)                | 8 (8)                         |

For antifungals without established epidemiological cutoff points, the points established in Table 1 (shaded area) have been taken into account.

*C. parapsilosis* is the first or second etiology of IC in China, Japan, Latin America, and the Mediterranean countries of Africa, Asia, and Europe, such as Italy, Portugal, and Spain (Quindós et al., 2018). In the current report, ibrexafungerp MICs ranged from 0.016 mg/L to 8 mg/L. Our results are in accordance to those by Marcos-Zambrano et al. (2017). In both studies, ibrexafungerp displayed remarkably lower MICs than micafungin against *C. parapsilosis*. Although Mesquida et al. (2022) did not differentiate among *C. parapsilosis* species complex, they also reported lower MICs for ibrexafungerp than for echinocandins. These high MIC values reported for echinocandins against *C. parapsilosis* have been associated with substitutions in the his1 region of *FKS1* (Garcia-Effron et al., 2008; Dudiuk et al., 2017; Marcos-Zambrano, 2017; Mesquida et al., 2022). Schell et al. (2017) also reported lower ibrexafungerp MIC<sub>50</sub> values for 19 *C. parapsilosis* blood isolates (0.25 mg/L) compared with echinocandins, suggesting that changes in *FKS1* may not affect the capacity of ibrexafungerp to inhibit glucan synthase in this species.

*C. glabrata* has increased its etiological importance in IC in Australia, Canada, the USA, and countries in Central and Northern Europe, such as Belgium and Germany (Quindós, 2014; Trouvé et al., 2017; Quindós et al., 2018). In our study, ibrexafungerp displayed potent activity (MIC range 0.016–8 mg/L) also against fluconazole-resistant isolates. No cross-resistance has been found between ibrexafungerp and fluconazole, as previously noted by Marcos-Zambrano et al. (2017). The incidence of echinocandin resistance in *C. glabrata* is generally considered low, approximately 3%–4%, but can be as high as 30% in specific institutions (Alexander et al., 2013; Pham et al., 2014; Arendrup and Patterson, 2017). In the current study, ibrexafungerp MIC was ≤4 mg/L against four *C. glabrata* resistant to both fluconazole and micafungin. Pfaller et al. (2013) found similar results to ours but, in their report, ibrexafungerp was 8-fold more active than caspofungin against *C. glabrata*. Furthermore, ibrexafungerp showed activity against 31 *C. glabrata* strains with mutations in the hs of *FKS1* or *FKS2* (MIC ≤ 2 mg/L) and against 14 strains resistant to both caspofungin and fluconazole. In a later study by the same authors (Pfaller et al., 2017), 20 out of 25 FKS mutant *C. glabrata* isolates (80%) were NWT to one or more echinocandins, but only six (24%) were NWT to ibrexafungerp. Isolates of *C. glabrata* for which the ibrexafungerp MIC was > 2 mg/L (NWT) all were NWT and either intermediate or resistant to anidulafungin, caspofungin, and micafungin. In our study, 3 out of 4 isolates potentially NWT for ibrexafungerp were inhibited by ≤1 mg/L of caspofungin and one by 0.03 mg/L of micafungin. However, three of these four ibrexafungerp NWT isolates were resistant to micafungin.

Schell et al. (2017) evaluated 34 echinocandin-resistant *C. glabrata* isolates along with 34 paired control *C. glabrata* isolates, observing that ibrexafungerp MICs for individual *C. glabrata* isolates tended to be three to five dilutions higher than those for the echinocandins. However, ibrexafungerp MICs trended in agreement with those for the echinocandins. These authors detected that *C. glabrata* isolates with *FKS1* or *FKS2* mutations or echinocandin resistance were inhibited by ≤4 mg/L of ibrexafungerp. Nunnally et al. (2019) also reported good ibrexafungerp activity against 89 *C. glabrata* isolates with *FKS1* or *FKS2* mutations that conferred resistance to at least one echinocandin. Ibrexafungerp MIC values ranged from <0.03 mg/L to 4 mg/L while caspofungin and micafungin MICs ranged from 0.03 to >16 mg/L and 0.008 to >16 mg/L, respectively. In the study by Mesquida et al. (2022), an isolate of *C. glabrata* that displayed an ibrexafungerp MIC of 2 mg/L and echinocandin NWT phenotype harbored a mutation at *FKS2*. The spectrum of resistance mutations found in *C. glabrata* suggested a partially overlapping but independent binding site for ibrexafungerp relative to echinocandins on glucan synthase as these drugs are structurally dissimilar and interact differently with the target (Jiménez-Ortigosa et al., 2014). Consequently, this potent in vitro activity for ibrexafungerp has been reported against *C. glabrata* isolates harboring *FKS1* and *FKS2* point mutations that cause echinocandin resistance (Marcos-Zambrano et al., 2017; Pfaller et al., 2017; Schell et al., 2017; Nunnally et al., 2019; Mesquida et al., 2022). Moreover,
the in vitro efficacy of ibrexafungerp has been supported by successful treatments in murine IC caused by C. glabrata resistant to echinocandins (Lepak et al., 2015; Wiederhold et al., 2018). In a murine model of IC caused by C. albicans, C. parapsilosis, or C. glabrata using an oral therapy with ibrexafungerp, Lepak et al. (2015) demonstrated that the AUC/MIC was the best pharmacodynamics parameter predicting clinical response. A MIC ≤ 1 mg/L obtained by CLSI would predict a clinical response using oral ibrexafungerp (Marcos-Zambrano et al., 2017).

In Asia, C. tropicalis was the second etiological agent of IC in many hospitals from China, India, Singapore, Thailand, and Taiwan (Quindós et al., 2018). We observed that ibrexafungerp MICs ranged from 0.06 mg/L to ≥ 8 mg/L for 40 C. tropicalis blood isolates, which confirms the consistently low ibrexafungerp MICs for azole-resistant C. tropicalis reported by Schell et al. (2017). Mesquida et al. (2022) found mutations in the FKS1 gene of two NWT isolates of C. tropicalis that resulted, in both cases, in ibrexafungerp MICs between 0.5 and 1 mg/L.

We observed high activity of ibrexafungerp against 29 C. krusei (MIC range 0.125–1 mg/L). Schell et al. (2017) reported ibrexafungerp MICs for six isolates of C. krusei (MIC range from 0.5 mg/L to 4 mg/L), which were higher than those for the other Candida species. These authors suggested that a naturally occurring unidentified substitution may be responsible for the reduced activity of ibrexafungerp on glucan synthase in C. krusei. However, it is unknown if this translates into clinical failure.

In a recent Spanish nationwide study on candidemia, C. orthopsilosis was the fifth most frequently isolated species, preceding C. krusei (Pemán et al., 2012). In the present study, ibrexafungerp showed good activity against 20 C. orthopsilosis (MIC range 0.06–4 mg/L). To our knowledge, this is the first study on in vitro activity of ibrexafungerp against C. orthopsilosis. The lack of previous reports in this regard precludes comparison. Differences in ibrexafungerp activity against the closely related species C. orthopsilosis and C. parapsilosis highlights the importance of a correct identification of the Candida species involved in invasive infections.

C. auris is an emerging pathogen that has been identified in many countries associated with high mortality and a marked ability to develop resistance to multiple commonly used antifungal agents and to withstand standard infection control practices (Larkin et al., 2017; Ruiz-Gaitán et al., 2017; Ruiz-Gaitán et al., 2018; Ruiz-Gaitán et al., 2019). Data from Larkin et al. (2017) show that the C. auris isolates exhibited multidrug resistance against fluconazole and amphotericin B. Moreover, some isolates also exhibited high MIC values for voriconazole and itraconazole. In the present report, all C. auris isolates were resistant to fluconazole while ibrexafungerp showed notable activity (MIC range 0.5 mg/L to 8 mg/L). The in vitro activity of ibrexafungerp against European C. auris isolates from our study was similar to that described by Berkow et al. (2017) who studied 100 isolates of this species from Asia, Africa, and America. Of note, in the current study, MM values between C. auris WT and NWT isolates increased 64-fold for caspofungin and 4-fold for micafungin, whereas MM values for ibrexafungerp did not change. Interestingly, ibrexafungerp has been shown to
Ibrexafungerp was twofold less active than caspofungin or micafungin against six *C. guilliermondii* blood isolates. Accordingly, Mesquida et al. (2022) also found higher ibrexafungerp MICs for 12 *C. guilliermondii* isolates, from 0.125 to 8 mg/L. Naturally occurring high echinocandins MICs against *C. guilliermondii* have been recognized since these antifungal agents were first introduced probably in association to substitutions in the hs1 region of *FKSI* (Dudiuk et al., 2017; Schell et al., 2017). In addition, Schell et al. (2017) reported that ibrexafungerp MIC ranges for three *C. lusitaniae* blood isolates were 1 to 2 mg/L and ibrexafungerp MICs for *C. lusitaniae* were three to five dilutions higher than those for the other species of *Candida*. Ibrexafungerp MICs for the two isolates of *C. lusitaniae* (MICs 4 and 8 mg/L) tested in the current study were higher than those observed for the other *Candida* species.

Aside from emerging resistance, an important limitation of echinocandins is that they must be administered daily by intravenous infusion, potentially prolonging hospital stays for patients undergoing echinocandin therapy and limiting them to inpatient settings in most instances. Of note, Wring et al. (2018) reported that the risk for interactions of ibrexafungerp with drugs metabolized via the cytochrome P450 family of enzymes is low. Ibrexafungerp exhibited concentration- and time-dependent fungicidal activity against *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis* in time-kill curve studies (Scoreaux et al., 2017). Moreover, ibrexafungerp has demonstrated efficacy for IC in phase 2 and 3 clinical studies (Spec et al., 2019).

The current study demonstrates that ibrexafungerp shows potent *in vitro* activity against *Candida* blood isolates and its activity is comparable to that of micafungin. Ibrexafungerp even exhibits good activity against fluconazole-resistant *Candida* isolates. Moreover, echinocandin-resistant isolates exhibit ibrexafungerp MICs consistent with those of echinocandin-susceptible isolates. However, direct comparisons of ibrexafungerp MICs with those of other antifungal drugs should be interpreted with caution, as different drugs may produce diverse ranges of MICs and yet have equivalent clinical efficacy because of their differences in bioavailability and in PK/PD properties. Although Pfaller et al. (2013) reported >90% essential agreement between both methods, CLSI and EUCAST, the comparison between our results and those of American authors should consider that the EUCAST method tends to yield higher MICs than CLSI, regardless of the studied species. Although the most clinically relevant species of *Candida* have been included in the current study, it would be interesting to assess the activity of ibrexafungerp against additional species as well as more NWT isolates.

In conclusion, we demonstrated that ibrexafungerp, a potent inhibitor of glucan synthase, could be an important acquisition to the antifungal toolbox for the therapy of patients suffering from IC caused by MDR species, such as *C. auris*, *C. glabrata*, or *C. krusei*. Considering the excellent pharmacokinetic properties of ibrexafungerp (oral availability and excellent tissue distribution and concentrations) as well as the potent activity observed against the main species causing candidiasis, ibrexafungerp should be regarded as a potential candidate for the therapy of these important diseases.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

**AUTHOR CONTRIBUTIONS**

GQ, KM-C, and RS-M designed the research and participated in manuscript writing. KB-E, EC, MJL-S, AH, IM, AT, AP, MV-G, CM-A, AG, FS-R, JM-B, MR-I, EM-M, CC-M, LL-S, AR-G, MF-R, DL, JC, AR, JaP, JG, JoP, CP, OR, GE, NJ, DA, and EE conducted sampling and clinical measures, carried out the experiments,
analyzed data, and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcimb.2022.906563/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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