Current Research in Microbial Sciences 6 (2024) 100245

Contents lists available at ScienceDirect

Current Research in Microbial Sciences

journal homepage: www.sciencedirect.com/journal/current-research-in-microbial-sciences

Ibrexafungerp: A narrative overview

L'Emir Wassim El Ayoubi [a], Fatima Allaw [a,1], Elie Moussa [b,1], Souha S. Kanj [a,c,*]

[a] Division of Infectious Diseases, American University of Beirut Medical Center, Beirut, Lebanon
[b] Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon
[c] Center for Infectious Diseases Research, American University of Beirut, Beirut, Lebanon

ARTICLE INFO

Keywords:
Ibrexafungerp
Invasive candidiasis
Vulvovaginal candidiasis
Candida auris
Invasive pulmonary aspergillosis

ABSTRACT

Ibrexafungerp (IBX) is a new antifungal drug that recently entered the antifungal landscape. It disrupts fungal cell wall synthesis by non-competitive inhibition of the β-(1,3)-D-glucan (BDG) synthase enzyme. It has demonstrated activity against a range of pathogens including *Candida* and *Aspergillus* spp., as well as retaining its activity against azole-resistant and echinocandin-resistant strains. It also exhibits anti-biofilm properties. Pharmacokinetic (PK) studies revealed favorable bioavailability, high protein binding, and extensive tissue distribution with a low potential for CYP-mediated drug interactions. It is characterized by the same mechanism of action of echinocandins with limited cross-resistance with other antifungal agents. Resistance to this drug can arise from mutations in the *FKS* genes, primarily *FKS2* mutations in *Nakaseomyces glabrata*. In vivo, IBX was found to be effective in murine models of invasive candidiasis (IC) and invasive pulmonary aspergillosis (IPA). It also showed promising results in preventing and treating *Pneumocystis jirovecii* infections. Clinical trials showed that IBX was effective and non-inferior to fluconazole in treating vulvovaginal candidiasis (VVC), including complicated cases, as well as in preventing its recurrence. These trials positioned it as a Food and Drug Administration (FDA)-approved option for the treatment and prophylaxis of VVC. Trials showed comparable responses to standard-of-care in IC, with favorable preliminary results in *C. auris* infections in terms of efficacy and tolerability as well as in refractory cases of IC. Mild adverse reactions have been reported including gastrointestinal symptoms. Overall, IBX represents a significant addition to the antifungal armamentarium, with its unique action, spectrum of activity, and encouraging clinical trial results warranting further investigation.

1. Introduction

Over the past years, there has been a notable rise in the prevalence of invasive fungal infections (IFI) worldwide, leading to increased healthcare expenditures and posing a significant threat to global health (Kmeid et al., 2020). The burden is particularly pronounced for individuals with compromised immune systems, such as those with malignancies or human immunodeficiency virus (HIV), as well as critically ill patients who are at high risk for developing IFI, leading to complications and, in severe cases, death (Wiederhold, 2021). The global impact of IFI is staggering, affecting over a billion individuals, and contributing to more than 1.5 million deaths annually (Bongomin et al., 2017). Furthermore, these infections pose a significant economic toll, with the estimated total cost of IFI in the United States of America (USA) alone reaching approximately $7.2 billion in 2019 (Benedict et al., 2019).

In addition to the rising incidence of fungal infections, partly

Abbreviations: AUC, area under the curve; BDG, β-(1,3)-D-glucan; CNS, central nervous system; *C*max, maximal plasma concentration; DRC, data review committee; ECCMID, European congress of clinical microbiology and infectious diseases; EMA, European medicines agency; FDA, food and drug administration; HIV, human immunodeficiency virus; IC, invasive candidiasis; IFI, invasive fungal infection; IBX, ibrexafungerp; IPA, invasive pulmonary aspergillosis; LAMB, liposomal amphotericin B; MEC, minimum effective concentration; MIC, minimal inhibitory concentration; MSG, mycoses study group; PD, pharmacodynamic; PK, pharmacokinetic; PCP, *Pneumocystis* pneumonia; POSA, posaconazole; SOC, standard-of-care; TOC, test-of-cure; USA, United States of America; UTI, urinary tract infection; VV, cvulvovaginal candidiasis.

* Corresponding author at: Professor of Medicine, Associate Vice President for Global Affairs, Head, Division of Infectious Diseases, Chairperson, Infection Control Program, Co-Director, Antimicrobial Stewardship Program, American University of Beirut Medical Center, Lebanon, Consultant Professor, Duke University Medical Center, USA, Honorary Dr., Radboud University Medical Center, NL, President-Elect, International Society of Antimicrobial Chemotherapy (ISAC), President, Lebanese Society of Infectious Diseases and Clinical Microbiology (LSIDCM), AUBMC, PO -Box 11-0236, Riad El Solh 1107 2020, Beirut, Lebanon.
E-mail address: sk11@aub.edu.lb (S.S. Kanj).
[1] Contributed equally.

https://doi.org/10.1016/j.crmicr.2024.100245

Available online 27 May 2024
2666-5174/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

attributed to the enhanced survival of patients at risk, the treatment of these infections is further complicated by the growing resistance to the currently used antifungal agents, making even the management of non-invasive fungal infections challenging. This resistance is multifactorial and mostly due to the extensive use of antifungal agents in healthcare settings as well as the application of antifungal pesticides for agricultural purposes (Verweij et al., 2009). Moreover, it is postulated that climate change and certain animal reservoirs contribute to antifungal resistance (Casadevall et al., 2019). *Candida* species, particularly *Candida albicans*, are the most common cause of IFI. However, a concerning increasing trend of non-albicans *Candida* spp. in some parts of the world with resistance to various antifungal drugs, predominantly azoles, has recently emerged. For instance, *Candida auris*, a newly identified spp. in 2009, recently became a major global concern due to its rapid spread, high mortality in invasive infections, and its inherent resistance to multiple antifungal agents including echinocandins and amphotericin B (Seagle et a., 2021; Ahmad and Alfouzan, 2021). Other important causative organisms of IFI include *Aspergillus* spp., with many isolates, notably *Aspergillus fumigatus,* becoming resistant to azoles (Wiederhold (2021). Resistance to azoles in *A. fumigatus*, often linked to chronic exposure, has been associated with point mutations within the CYP51A gene (Seyedmousavi et al., 2014), with some cases unrelated to prior azole exposure, suggesting alternative routes of resistance development (Verweij et al., 2009; Snelders et al., 2009; Resendiz Sharpe et al., 2018; Wiederhold, 2021).

In view of the rising multidrug-resistant fungal species, and limitations posed by cost, toxicity, and the parenteral route of administration for existing options, the need for novel agents in the antifungal armamentarium is undeniable. Ibrexafungerp (IBX), an oral first-in-class drug, initially solely approved by the Food and Drug Administration (FDA) for vulvovaginal candidiasis (VVC), has demonstrated promise for broader applications (Seiler and Ostrosky-Zeichner, 2021).

This review delves into IBX's mechanism of action and mechanisms of resistance, its pharmacokinetic (PK)/ pharmacodynamic (PD) properties and safety profile, its spectrum of activity, and examines the latest clinical trials and real-world data evaluating its efficacy in the treatment of various fungal species and infection sites. Additionally, it explores its current applications and potential future roles in clinical practice.

2. Mechanism of action and resistance

IBX is the first drug in a novel antifungal class known as triterpenoids, resulting from modifications made to the naturally occurring hemiacetal triterpene glycoside, enfumafungin, thus making IBX its semi-synthetic derivative (Angulo et al., 2022). Its mode of action is illustrated in Fig. 1. It involves the inhibition of β-(1,3)-D-glucan (BDG) synthesis in the fungal cell wall (Apgar et al., 2021). BDG is an essential component of the fungal cell wall and a main molecule in numerous fungi, making it a crucial therapeutic target (Garcia-Rubio et al., 2019). IBX acts through non-competitive inhibition of the BDG synthase enzyme, an enzyme complex composed of various subunits encoded by different genes, such as *FKS1, FKS2, FKS3*, and *Rho1p* (Jallow and Govender, 2021). It is noteworthy that echinocandins share a similar mechanism of action by inhibiting the same enzyme (Walker et al., 2011). IBX's mechanism of action leads to an increased permeability of the fungal cell wall, resulting in cell lysis due to osmotic stress. Similar to echinocandins, IBX is fungicidal against *Candida* spp. (Scorneaux et al., 2017) but fungistatic against *Aspergillus* spp. (Ghannoum et al., 2018). Distinct advantages of IBX over echinocandins include its oral bioavailability, larger volume of distribution, and limited cross-resistance in strains resistant to echinocandins. This is attributed to the fact that IBX binding sites on the synthase enzyme differ from those of echinocandins, with only a partial overlap (Walker et al., 2011; Davis, Donnelley, and Thompson 2020).

The widespread use of echinocandins has resulted in resistance in several *Candida* spp., particularly in isolates of *Nakaseomyces glabrata* (formerly *C. glabrata)* and *C. auris* (Alexander et al., 2013; Kordalewska et al., 2018; Naicker et al., 2016). This resistance arises from mutations in the *FKS* genes, which code for the catalytic site of the BDG synthase enzyme complex. Notably, IBX maintains potent activity against echinocandin-resistant *N. glabrata* with *FKS* mutations (Nunnally et al., 2019). However, some *FKS* mutant isolates exhibit increased IBX minimal inhibitory concentration (MIC) values, leading to a 1.6 –16-fold decrease in IBX susceptibility (Jimenez-Ortigosa et al., 2017). Deletion

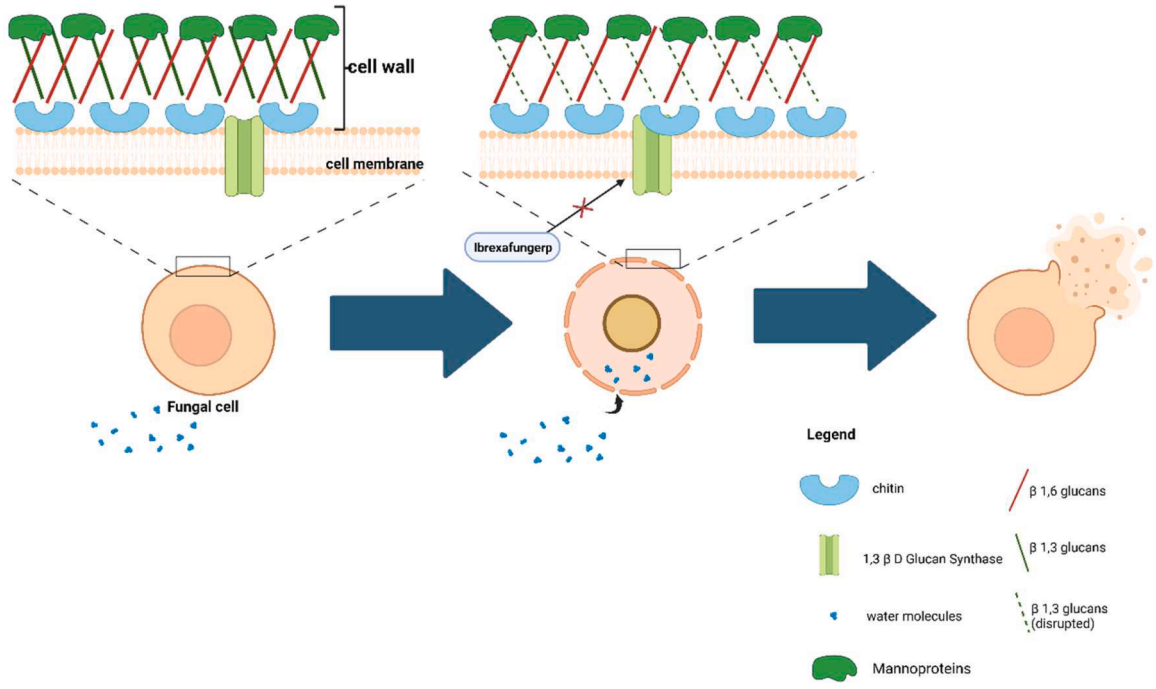

Fig. 1. Ibrexafungerp is a β-(1,3)-D-glucan (BDG) synthase inhibitor, an enzyme involved in the production of BDG. BDG is a vital cell wall component. In its absence, the cell wall becomes fragile, exposing the fungal cell to excessive osmotic stress, leading to osmotic lysis.

mutations in the *FKS1* (*F625del*) and *FKS2* genes (*F659del*) lead to 40-fold and >121-fold increases in the MIC_{50} for IBX, respectively, which are attributed to a change in the enzyme's amino acid sequence, reducing IBX's binding ability (Jimenez-Ortigosa et al., 2017). Most mutations associated with IBX resistance in *N. glabrata* are in the *FKS2* gene, suggesting that the synthesis of BDG in *N. glabrata* is primarily encoded by the *FKS2* gene (Jimenez-Ortigosa et al., 2017; Perlin, 2007). While extensive research has been done on IBX's in vitro activity against resistant isolates, none of the studies explore the rate of developing resistance to this new antifungal agent among these isolates.

3. Spectrum of activity

As previously discussed, similar to echinocandins, IBX is an inhibitor of BDG synthesis, a vital cell wall component in most of the clinically significant fungal species (Chen, Slavin, and Sorrell 2011). Its efficacy aligns with the abundance of BDG within the fungal cell wall. IBX has been found to be potent against most *Candida* spp. (Quindos et al., 2022), *Aspergillus* spp. (Pfaller et al., 2013), and has exhibited anti-biofilm properties in various *Candida* spp., including *C. auris* and *N. glabrata* (Larkin et al., 2017; Nunnally et al., 2019; Marcos-Zambrano et al., 2017). However, an exception to this broad spectrum of activity would be *Cryptococcus neoformans,* which, despite its BDG-rich wall, exhibits resistance to BDG synthase inhibitors. The specific interaction between IBX and *Cryptococcus neoformans* remains to be explored (Hoenigl et al., 2021). IBX has also demonstrated activity against the ascus forms of *Pneumocystis* spp., enabling it to control colonization/infection without complete eradication (Porollo et al., 2012). Interestingly, IBX displays low cross-resistance with echinocandins, indicating distinct binding sites (Walker et al., 2011). Furthermore, it manifests efficacy against azole-resistant isolates (Nunnally et al., 2019; Jimenez-Ortigosa et al., 2014; Pfaller et al., 2017), including pan-resistant strains (Zhu et al., 2020). This dual capability of broad-spectrum coverage and effectiveness against resistant isolates underscores its pivotal role in the antifungal arsenal.

3.1. In vitro activity

3.1.1. Candida species

IBX has shown activity against various *Candida* spp. (Schell et al., 2017). Its effectiveness against *C. lusitaniae* and *P. kudriazvcevii* appears relatively diminished. Particularly noteworthy is its demonstrated activity against the emerging pathogen, *C. auris* (Berkow et al., 2017; Arendrup et al., 2020), a fungus labeled as a critical priority pathogen by the WHO (2022). Not only does IBX kill *C. auris* yeast, but it also has inhibitory effects on *C. auris* growth and division, suggesting additional targets beyond BDG synthase (Larkin et al., 2017). While IBX displays potent fungicidal activity against azole-resistant *Candida* isolates (Schell et al., 2017), it displays variable efficacy against echinocandin-resistant strains according to the species at hand and the mutation it is carrying, which was further validated in a study conducted in 2024 (Pfaller et al., 2017; Aldejohann et al., 2024). In fact, studies on *N. glabrata* and *C. albicans* indicate that specific amino acid sequence-altering *FKS* mutations such as *F641S* in *C. albicans*, and *F649del, F658del, F659S, F659del, E655A*, and *W715L* in *N. glabrata*, decrease the susceptibility of these microorganisms to IBX (Nunnally et al., 2019; Mesquida et al., 2022). IBX displayed higher MIC values as compared to echinocandins for *Candida* spp. except for *C. parapsilosis*., however, further clinical correlation is needed (Pfaller et al., 2017). Interestingly, IBX has also displayed anti-biofilm activity, through the inhibition of an essential component of this complex (Marcos-Zambrano et al., 2017; Larkin et al., 2017).

3.1.2. Molds

IBX showcases activity against various *Aspergillus* spp. (Pfaller et al., 2013), albeit with a fungistatic rather than a fungicidal effect. For *Aspergillus* spp., the MIC may be misleading, as IBX disrupts hyphal growth through hyphal tip lysis. Consequently, a more suitable measure to monitor susceptibility would be the minimum effective concentration (MEC), indicating the minimal concentration at which abnormal hyphal growth occurs (Odds et al., 2003). IBX has proved to be active against various *Aspergillus* spp., including azole-resistant isolates (Pfaller et al., 2013; Jimenez-Ortigosa et al., 2014; Rivero-Menendez et al., 2021). Although echinocandin-resistant *Aspergillus* spp. are rarely encountered (reported to be secondary to an *S678 ER* mutation), IBX displays activity against these variants (Rocha et al., 2007; Jimenez-Ortigosa et al., 2014). Early data from 2015 showed that IBX exhibits minimal to no activity against *Mucorales* and *Fusarium* spp. (Lamoth and Alexander, 2015). However, recent results presented at the European Congress of Clinical Microbiology and Infectious Diseases's (ECCMID) 33rd congress in 2023 demonstrated a significant reduction in the fungal growth of *Rhizopus* spp. on scanning electron microscopy when IBX was combined with either liposomal amphotericin B (LAMB) or posaconazole (POSA) (Long et al., 2023). IBX has also demonstrated efficacy against other molds, notably high activity against *Alternaria* spp. and *Cladosporium* spp. and marginal activity against *Lomentospora prolificans, Scedosporium* spp. and *Scopulariopsis* spp. (Angulo et al., 2022).

3.2. In vivo activity

IBX's in vivo efficacy extends across multiple fungal species and clinically relevant sites. In murine models of invasive candidiasis (IC), it has proven to be effective against various *Candida* spp. including *N. glabrata, C. parapsilosis,* and *C. albicans* (Lepak et al., 2015; Wring et al., 2017), some of which were azole-resistant and echinocandin-resistant (Wiederhold et al., 2018). Additionally, IBX has shown activity against *C. auris* in a guinea pig model of cutaneous infection, with treated guinea pigs manifesting no fungal elements upon histopathological examination at the end of treatment (Ghannoum et al., 2020b). Notably, IBX not only proved to be effective against diverse *Candida* spp., but also demonstrated high penetration and accumulation in challenging sites, as evidenced in the intra-abdominal candidiasis murine model (Lee et al., 2020).

IBX's efficacy against *Aspergillus* spp. is evident in in vivo models (Borroto-Esoda et al., 2017), with optimal outcomes achieved when used in combination. In a neutropenic rabbit model of invasive pulmonary aspergillosis (IPA), IBX combined with isavuconazole improved survival and reduced fungal burden synergistically (Petraitis et al., 2020). This synergistic effect is further confirmed in another study, where IBX combined with amphotericin B was found to be superior to either drug used alone in the treatment of resistant CYP51A mutants (Ghannoum et al., 2018).

IBX was also found to be effective in the treatment of *Pneumocystis jirovecii* in a *Pneumocystis* pneumonia (PCP) murine model. However, it falls short of trimethoprim-sulfamethoxazole in terms of outcomes (Barat et al., 2019). Moreover, IBX has also demonstrated the ability to prevent PCP when administered prophylactically in a murine model (Borroto-Esoda et al., 2020).

Despite limited data on IBX in vitro activity against *Mucor* spp., a study presented at the 32nd ECCMID conference in 2022, showed that IBX in combination with LAMB and POSA improved survival time and showed similar effectiveness to LAMB or POSA alone in prolonging the median survival time of neutropenic murine models with pulmonary mucormycosis (Gebremariam et al., 2022).

4. Pharmacokinetics and pharmacodynamics

4.1. Absorption

IBX showed favorable bioavailability both in vitro and in vivo. Single oral doses in murine IC models achieved bioavailability values of 45–51 and 35 % in rodents and dogs respectively (Wring et al., 2017).

Maximum plasma concentrations (Cmax) were attained between 4 to 6 h after oral administration (Wring et al., 2017). In a phase I study involving healthy male volunteers, oral administration of IBX with doses ranging from 10 to 1600 mg, resulted in a roughly 20 % increase in both Cmax and area under the curve (AUC) when accompanied by a high-fat meal. The median time to reach Cmax ranged from 4 to 6 h post-dose. A subsequent phase I study in healthy volunteers ($n = 32$) assessed IBX's safety, tolerability, and pharmacokinetics (PK) with daily doses of 300 mg, 600 mg, 800 mg for 10 days, and 800 mg daily for 28 days. Steady-state was achieved after 2 weeks, and the half-life on day 10 was around 30 h. Mean AUC 0–24 values on day 10 varied among dose groups, reaching 45.77 μM h in the 800 mg group on day 26 (Trucksis et al., 2011).

Moreover, data revealed that using the citrate salt of IBX significantly enhances its solubility (Wring et al., 2017). Nonetheless, co-administration with pantoprazole 40 mg for 5 days resulted in a 25 % decrease in exposure compared to IBX administered alone (Davis et al., 2020). Taking the drug with food has the potential to enhance its dissolution in gastric and intestinal fluid, thereby increasing systemic absorption.

4.2. Distribution

IBX is a lipophilic compound, leading to a high estimated protein-binding within the range of 99.5 % to 99.8 % (Wring et al., 2017). Wring and colleagues demonstrated a substantial volume of tissue distribution at steady-state (5.3, 4.7, and 5.1 L/kg in mice, rats, and dogs, respectively). Particularly, distribution in kidney tissues exceeded plasma levels by 20 to 25-fold for AUC from 0 h to infinity and maximum concentration (Wring et al., 2017). This significant volume of distribution suggests that IBX binds to proteins with low affinity. Furthermore, IBX primarily binds to plasma proteins and not erythrocytes, highlighting its suitability for treating IC.

Additionally, it has been suggested that IBX may attain favorable free drug AUC (fAUC)/MIC ratios in pulmonary tissues, making it a potential candidate for use in the prophylaxis or treatment of pulmonary fungal infections (Davis et al.,2020). In a single dose PK analysis conducted in rats for invasive fungal disease, the tissue-to-blood ratios for various organs, listed from highest to lowest, were as follows: spleen 54, liver 50, lung 31, bone marrow 25, kidney 20, skin 12–18, vaginal tissue 9, and skeletal muscle 4. Notably, minimal distribution, if any, occurred in central nervous system (CNS) tissues and the spinal cord; with limited distribution to adipose tissues and variable distribution to the eye (none to the lens; high to the uvea) (Wring et al., 2019b).

4.3. Metabolism

Intravenous delivery of 1 mg/kg in mice and 5 mg/kg in rats and dogs resulted in low plasma clearance in rodents (<15 %) and dogs (<25 %), coupled with a prolonged half-life of 5.5 to 8.7 h in rodents and 9.3 h in dogs. In healthy humans, the mean terminal half-life varied between 20 and 30 h, thereby supporting the adoption of a once-daily dosing strategy (Trucksis et al., 2011, 2010). Furthermore, in a study done in rats involving a single IBX dose, minimal IBX recovery occurred in the urine (1.5 %), with predominant recovery observed in the feces and bile (90 %) (Wring et al., 2019a).

4.4. Drug-drug interaction and tolerability

The most common adverse effects associated with higher doses and longer duration of therapy of IBX included nausea, vomiting, abdominal pain, and diarrhea (Davis et al., 2020; Alexander et al., 2020). Notably, these effects were well-tolerated and non-serious events were observed. Moreover, IBX did not exhibit a clinically relevant impact on QTc interval in healthy volunteers (Murphy et al., 2017).

IBX functions as a substrate for CYP34A and acts as a reversible inhibitor of CYP2C8 (Wiederhold, 2022). In a phase 1, open-label, 2-period crossover study evaluating its interaction with rosiglitazone, a CYP2C8 substrate, IBX co-administration demonstrated no significant alteration in rosiglitazone exposure or its metabolite, *N*-desmethyl rosiglitazone, including maximum concentration values (Wring et al., 2018). This suggests a low risk for CYP-mediated drug interactions. Another open-label phase 1 study, examining the drug-drug interaction between IBX and tacrolimus (CYP34A substrate), revealed very little interaction between the 2 drugs at therapeutic levels of IBX (Wring et al., 2019b). However, other phase 1 studies showed that IBX AUC increased by more than 5-fold when co-administered with ketoconazole (a potent CYP3A inhibitor) and over 2-fold when co-administered with diltiazem (a moderate CYP3A inhibitor) (Murphy et al., 2017). Consequently, while dose adjustments may be necessary for potent CYP3A4 inhibitors, IBX exhibits limited potential for interaction with drugs metabolized by CYP450.

As for its teratogenicity, animal studies have revealed that IBX has potential embryotoxicity, leading the FDA to issue a warning against its use in pregnant women (FDA, 2021). An observational study assessing its safety in pregnant women is currently underway (ClinicalTrials.gov, 2023).

4.5. Landmark preclinical studies about animal models and in vivo efficacy

The initial PD evaluation was conducted in a study involving a neutropenic IC murine model. The static and 1-log kill doses, as well as the total and fAUC/MIC, showed no statistical differences between *C. albicans, N. glabrata*, and *C. parapsilosis*. However, these values were found to be lower than those observed for echinocandins (Lepak et al., 2015). The fAUC/MIC values linked to achieving a 1-log kill reduction in fungal burden for these species were 1.42, 1.26, and 0.91 respectively (Lepak et al., 2015). In the same study, oral doses of IBX ranging from 3.125 to 200 mg/kg resulted in peak concentrations of 0.04–2.66 μg/mL, AUC from 0 to 24 h of 0.61–41.10 μg h/mL, and AUC from 0 h to infinity values of 0.68–40.31 μg h/mL (Lepak et al., 2015).

Another murine study, investigating steady-state exposure in plasma and kidney tissue after twice-daily treatment for a week, revealed that IBX achieved efficacy with a mean plasma steady-state AUC of 15.4 ± 2.21 μM h and a corresponding total drug AUC/MIC ratio of 373 ± 54. Kidney tissue exposure exceeded plasma by over 20-fold for both AUC from 0 h to infinity and maximum concentration. The drug exhibited higher kidney/plasma exposures which might explain the lower fAUC/MIC in blood compared to echinocandins (Wring et al., 2017).

5. The clinical evidence so far

As of the writing date of this manuscript, IBX has been evaluated in a total of 16 trials, 13 of which have been completed. A concise overview of the designs, endpoints, and results of trials evaluating its clinical efficacy are provided in Table 1. Given its broad spectrum of activity, IBX is being assessed for multiple conditions with various sites of infection, ranging from VVC to IC, as well as endemic mycoses such as blastomycosis and coccidioidomycosis. This section will cover the clinical efficacy of IBX.

5.1. Vulvovaginal candidiasis

VVC is the second most common cause of vaginitis (Achkar and Fries, 2010) affecting over 75 % of women during their childbearing years (Sobel, 2007) with 5 to 9 % experiencing recurrent episodes (Denning et al., 2018). Historically, azoles have been the primary antifungal class for treating VVC (Pappas et al., 2016), however, with increasing reports of azole resistance in *Candida* spp., IBX has emerged as a promising addition to the treatment arsenal especially given that it can be administered orally (Nyirjesy et al., 2022a).

Table 1
Clinical trials involving Ibrexafungerp in various indications.

Main focus	NCT number	Study title	Acronym	Study design	Phase	Start date-completion date	Primary outcome (s)	Secondary outcome(s)	Study status	Study results	Limitations
Vulvovaginal candidiasis	NCT05399641	Ibrexafungerp for the Treatment of Complicated Vulvovaginal Candidiasis	VANQUISH	Randomized, parallel-assignment open-label study	Phase 3	05/01/2022-6/30/2024	Clinical cure at the TOC visit 14 Days post-baseline	-Clinical improvement (day 14 to day 60) -Clinical success (day 16 to day 60)	Active - Not Recruiting		-Patients below 18 years were excluded -immunocompromised patients were not included -Study was not blinded
	NCT04029116	Phase 3 Study of Oral Ibrexafungerp (SCY-078) Vs. Placebo in Subjects with Recurrent Vulvovaginal Candidiasis (VVC)	CANDLE	Multicenter, randomized, triple-blind, placebo-controlled study	Phase 3	10/21/2019-11/29/2021	-Clinical success -Clinical success (week 24)	-No mycological recurrence by week 24 -Safety and tolerability	COMPLETED	Clinical success: IBX:65.4 % Placebo: 53.1 % No mycological recurrence: -IBX:82 % -Placebo:73 %	-Patients below 18 years of age were not adequately represented
	NCT03987620	Efficacy and Safety of Oral Ibrexafungerp (SCY-078) vs. Placebo in Subjects with Acute Vulvovaginal Candidiasis	Vanish 306	Randomized, multicenter, double-blind, placebo-controlled study	Phase 3	06/07/2019-4/29/2020	Clinical cure TOC visit (day 8-14)	-Mycological eradication at TOC visit -Clinical cure and mycological eradication at TOC visit -Complete clinical response at follow-up -Safety and tolerability of IBX	COMPLETED	Clinical Cure: -IBX:63.3 % -Placebo:44 % Clinical Improvement: -IBX:72.3 % -Placebo:54.8 % Clinical cure (day 25): -IBX:73.9 % -Placebo:52.4 %	-Use of a placebo arm -Lack of racial/ethnic diversity -Low number of patients with a body mass index >35 - Patients below 18 years were excluded -Small number of patients with *Candida* non-albicans infections
	NCT03734991	Efficacy and Safety of Oral Ibrexafungerp (SCY-078) vs. Placebo in Subjects with Acute Vulvovaginal Candidiasis (VANISH 303)	Vanish 303	Randomized, multicenter, Triple-blind, placebo-controlled study	Phase 3	01/04/2019-9/04/2019	Clinical cure at TOC visit (days 8-14)	-Mycological eradication at TOC visit Clinical and mycological cure at TOC visit -Complete clinical response at follow-up -Treatment-related AEs	COMPLETED	Clinical cure at TOC visit: -IBX:50.5 % -Placebo: 28.6 % Mycological eradication: -IBX:49.5 % -Placebo:19.4 % Clinical cure (day 25): -IBX:59.6 % -Placebo:44.9 %	-Patients below 18 years were excluded -Use of a placebo arm -Small number of patients with non-albicans *Candida* infections
	NCT03253094	Dose-Finding Study of Oral Ibrexafungep (SCY-078) vs. Oral Fluconazole in Subjects with Acute Vulvovaginal Candidiasis	DOVE	Multicenter, randomized, quadruple-blind, double-dummy, active-controlled, dose-finding study	Phase 2	08/01/2017-05/04/2018	Clinical Cure at TOC visit (day 10)	-Clinical and mycological cure at TOC	COMPLETED	Clinical cure: -IBX: 51.9 % -Fluconazole:58.3 % clinical cure (day 25): -IBX: 70.4 % -Fluconazole: 50 % Need for rescue antifungal: -IBX:3.7 % -Fluconazole:29.2 %	-Sample sizes for the treatment groups were small -Patients in the study received only 1 dose of fluconazole, while current practice guidelines recommend patients to receive 2–3 doses of fluconazole for patients with severe VVC
Invasive candidiasis	NCT05178862	A Phase 3, Randomized, Double-blind Study for	MARIO -MSG-20	Multicenter, prospective, randomized,	Phase 3	08/03/2022-08/2024	-All-cause mortality Day 30	-Global response at day 14	SUSPENDED		-Various sites of IC not included

(*continued on next page*)

Table 1 (*continued*)

Main focus	NCT number	Study title	Acronym	Study design	Phase	Start date-completion date	Primary outcome (s)	Secondary outcome(s)	Study status	Study results	Limitations
		Patients with Invasive Candidiasis Treated With IV Echinocandin Followed by Either Oral Ibrexafungerp or Oral Fluconazole		double-blind Study			-Global response at EoT				
	NCT03363841	Open-Label Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY-078) in Patients with Candidiasis Caused by *Candida auris* (CARES)	CARES[a]	Multicenter, open-label, non-comparator, single-arm study	Phase 3	11/15/2017-5/24/2023	-Global success (complete or partial response) at EoT	-Treatment-related AE -Treatment discontinuation due to AE -Recurrence of fungal infection -Survival	COMPLETED	-10 patients (finished treatment October 2020): complete response: 80 % Side effects:20 % -18 patients (finished treatment by October 2021): complete/partial response: 72 % Stable disease: 11 % 1 death, unrelated to fungal disease -5 patients (C. auris UTI): complete/partial response:100 %	-Not blinded -No comparator arm
	NCT02244606	Oral Ibrexafungerp (SCY-078) vs. Standard-of-Care Following IV Echinocandin in the Treatment of Invasive Candidiasis	MSG -10	Open-label, randomized study	Phase 2	09/2014-08/2016	-Safety and tolerability -Dose of SCY-078 that achieves the target exposure (AUC)	-Global response -Clinical response -Microbiological response -Relapse (2- and 6-weeks post-treatment)	COMPLETED	Global response: -IBX 500:71 % -IBX 750:86% -Fluconazole:75 % Global response (at 2 weeks): -IBX 500:57 % -IBX 750:57 % -Fluconazole:71 % Global response (at 6 weeks): -IBX 500:43 % -IBX 750:29 % -Fluconazole:57 %	-Small sample size
Invasive aspergillosis	NCT03672292	Study to Evaluate the Safety and Efficacy of the Coadministration of Ibrexafungerp (SCY-078) With Voriconazole in Patients with Invasive Pulmonary Aspergillosis	SCYNERGIA	Multicenter, randomized, quadruple-blind, two-arm study	Phase 2	1/22/2019-3/27/2023	-AEs -Discontinuation due to AE -Death	-Global response -Death (day 42 to day 84) -Study drug and comparator plasma concentration	COMPLETED		
Multiple conditions (VVC,IC, IPA, endemic mycoses)	NCT03059992	Study to Evaluate the Efficacy and Safety of Ibrexafungerp in Patients with Fungal Diseases That Are Refractory to or	FURI[b]	Multicenter, open-label, non-comparator, single-arm study	Phase 3	04/01/2017-8/17/2023	Global Response at EoT	-Recurrence of baseline fungal infection -Survival (day 42 to day 84)	COMPLETED	-20 patients (Invasive candidiasis): complete response: 55 % Stable disease: 30 %	

(*continued on next page*)

Table 1 (*continued*)

Main focus	NCT number	Study title	Acronym	Study design	Phase	Start date-completion date	Primary outcome (s)	Secondary outcome(s)	Study status	Study results	Limitations
		Intolerant of Standard Antifungal Treatment								Progressive disease: 10 % -33 patients (15 Invasive candidiasis,9 mucocutaneous candidiasis, 3 invasive aspergillosis: clinical improvement, complete/partial response: 70 % Stable disease: 21 %	

VVC, Vulvovaginal candidiasis; IC, Invasive candidiasis; IPA, Invasive pulmonary aspergillosis; TOC, Test-of-cure; EoT, End of treatment; AUC, Area under the curve; AE, Adverse events.
a, b: preliminary data presented in international conferences.

IBX was initially evaluated in the DOVE trial, a randomized phase 2 quadruple-blind clinical trial that enrolled 186 patients (Nyirjesy et al., 2022b). After randomization into groups with varying doses and durations of IBX, the optimal dose with the least side effects while preserving efficacy was determined to be 300 mg twice daily for one day. The optimal dose exhibited a clinical cure rate on test-of-cure (TOC) day (on day 10) similar to fluconazole (51.9 % vs. 58.3 %, respectively), establishing IBX's non-inferiority to the standard of care (SOC). Additionally, IBX-treated patients showed a sustained response, with fewer signs or symptoms on Day 25 (70.4 % vs. 50 %, respectively) and a lower requirement for antifungal rescue medications compared to fluconazole (3.7 % vs. 29.2 %, respectively) (Nyirjesy et al., 2022b). Thus, IBX's efficacy and safety in comparison to fluconazole for treating moderate-to-severe VVC was evident. Although IBX-treated patients were more likely to experience side effects (46.7 % vs. 25 %, respectively), these were generally mild gastrointestinal symptoms that resolved within a day (Nyirjesy et al., 2022b).

Following the determination of the optimal dose, IBX was further evaluated in the VANISH 303 trial, a phase 3, triple-blind, randomized, placebo-controlled superiority trial involving 376 patients with VVC. Results indicated that IBX was significantly more effective than placebo, with high rates of clinical cure at the TOC visit on day 10 (50.5 % vs. 28.6 %, respectively ($p = 0.001$)) mycological eradication (49.5 % vs. 19.4 % ($p<0.001$)) and sustained response on day 25 (59.6 % vs. 44.9 % ($p = 0.009$)) compared to placebo. Adverse events were mainly mild gastrointestinal symptoms (Schwebke et al., 2022). These findings were subsequently validated in the VANISH 306 trial, a global phase 3 double-blind randomized clinical trial that took place at multiple sites in the USA and Bulgaria, where IBX outperformed placebo in terms of clinical cure (63.3 % vs. 44 % ($p = 0.007$), mycological eradication (58.5 % vs. 29.8 % $p < 0.001$), clinical improvement (72.3 % vs. 54.8 % $p = 0.01$), and sustained response at follow -up (73.9 % vs. 52.4 % $p = 0.001$) (Sobel et al., 2022). A recent pooled analysis of both the VANISH 303 and 306 studies further supported IBX's efficacy and safety (Goje et al., 2023).

Having established its efficacy in treating acute VVC, IBX was then evaluated for its capacity to prevent recurrent episodes of VVC in the CANDLE trial. This multicenter phase 3, double-blind placebo-controlled trial involving 260 women above 12 years of age with recurrent VVC (defined as more than 3 episodes in the past year) demonstrated that IBX, given orally at 300 mg twice daily every 4 weeks for 6 doses, was effective in preventing recurrences, with 65.4 % of patients experiencing no recurrence compared to 53.1 % in the placebo group at week 24. Moreover, 70.8 % of patients taking IBX had no mycologic recurrence, compared to 58.5 % in the placebo group. IBX was well-tolerated, with only mild reported side effects, primarily headaches (20 %) and gastrointestinal symptoms (18.45 %) (ClinicalTrials.gov, 2019a).

Despite its tolerability and superiority in treating acute VVC and preventing VVC, these trials had limitations. None of these trials, despite defining patients over 12 years of age as one of their criteria, were able to enroll any patient below the age of 18. Furthermore, patients with uncontrolled diabetes mellitus or immunocompromised states including those affected by HIV, both of which are well-established risk factors for VVC, were excluded from the studies (CDC, 2022a).

The VANQUISH trial is an ongoing trial assessing IBX's ability to treat complicated VVC, with results expected by June 20, 2024. Complicated VVC is defined as patients with persistent symptoms despite being on fluconazole, patients with recurrent VVC and a breakthrough infection despite being on maintenance therapy, and patients with VVC secondary to non-*albicans* spp. with known intrinsic resistance to azoles or with suspected or documented resistance (ClinicalTrials.gov, 2022a).

5.2. Invasive candidiasis

In all its potential forms such as candidemia, endocarditis, and osteomyelitis, IC is a potentially life-threatening condition that is increasingly reported in hospitals worldwide and is emerging as one of the most common causes of bloodstream infections (Wisplinghoff et al., 2004). It is characterized by a high mortality rate, reported to be as high as 70 % in bloodstream infections (Falagas et al., 2006). While *C. albicans* remains the most common cause of IC, *non-albicans* spp. account for more than 60 % of cases, with a rise in intrinsically resistant species (Astvad et al., 2018). *C. auris* is of particular concern due to its highly resistant profile, with multi-drug resistant and pan-drug resistant isolates reported worldwide (Chowdhary et al., 2017). Given these therapeutic challenges, IBX's broad spectrum of activity, including resistant fungi, appears to be of particular interest.

The first trial to publish its results was the Mycoses Study Group (MSG)-10, a phase 2 multinational open-label randomized clinical trial. This trial aimed to evaluate IBX's efficacy and safety in treating patients with IC, comparing it to the SOC as step-down therapy from intravenous echinocandins. Additionally, the trial sought to determine the most effective IBX dose for treating IC. Among the 27 patients enrolled in the study, 22 were included, 7 of which were randomized to receive a 1250 mg loading dose of IBX followed by 750 mg once daily, another 7 to receive a 1000 mg loading dose of IBX followed by 500 mg once daily and the remaining 8 to receive either fluconazole ($n = 7$) or continue IV micafungin (=8) therapy. In an intention-to-treat analysis at the end of treatment, in terms of global response (both clinical and microbiological response), the 500 mg IBX group and 750 mg IBX group showed a similar response to the SOC group (71 % vs. 86 % vs. 75 %, respectively). However, during the follow-up evaluations, the global response was found to be lower at 2 weeks (57 % vs. 57 % vs. 71 %) and at 6 weeks (43 % vs. 29 % vs. 57 %) post-therapy. Notably, only one patient, belonging to the 500 mg IBX arm, experienced a relapse, but this recurrence was attributed to the placement of a biliary stent. Regarding safety, the observed outcomes were consistent with other trials assessing IBX, revealing that 10 % of study participants experienced mild gastrointestinal symptoms. PK studies further indicated that a loading dose of 1250 mg followed by 750 mg resulted in better drug exposure (Spec et al., 2019). Six *Candida* isolates were found to be *P. kudriazvcevii* or *N. glabrata*, with favorable outcomes also reported.

Another phase 3 multicenter randomized double-blind clinical trial conducted by the MSG, known as MSG-20 or MARIO, assessed oral IBX as step-down therapy after intravenous echinocandin therapy, comparing it to oral fluconazole in patients with IC (excluding patients with septic arthritis in a prosthetic joint, osteomyelitis, endocarditis or myocarditis, meningitis, endophthalmitis, CNS infection, chronic disseminated candidiasis, and urinary tract candidiasis). However, the study was suspended due to cross-contamination of the drug with a non-antibacterial beta-lactam drug substance. (ClinicalTrials.gov, 2022b).

The CARES trial is an ongoing multicenter, open-label, single-arm clinical trial aiming to evaluate the efficacy and safety of oral IBX in patients with *C. auris* infection (ClinicalTrials.gov, 2017a). Preliminary results from this trial have been published, revealing IBX's efficacy and tolerability in treating infections secondary to *C. auris* (Ghannoum et al., 2020a; Juneja et al., 2021; Siebert et al., 2022). Initial results from this trial, presented at ECCMID in 2020, highlighted two cases (Ghannoum et al., 2020a). The first involved a 64-year-old woman initially admitted for fever, hypotension, and pneumonia who developed *C. auris* candidemia. After starting IBX, her blood cultures turned negative on day 9, completing a 22-day course with a documented negative blood culture one day before the end of the treatment course and with no reported drug-related adverse events. The second case was a 58-year-old man admitted for septic shock, developing *C. auris* candidemia refractory to 5 days of intravenous micafungin. Switching to oral IBX led to negative blood cultures after 3 days, completing a 17-day course (Ghannoum et al., 2020a). More recent preliminary data from the CARES trial, published in 2021, revealed promising results; an independent data review committee (DRC) assessed 10 patients who completed therapy by October 2020 in 4 centers in South Asia and Africa, showing an 80 % complete response, with only 2 subjects experiencing gastrointestinal side effects (Juneja et al., 2021). Moreover, the efficacy and tolerability of IBX have consistently been demonstrated in recent reports across various *Candida* infection sites. An independent DRC assessment on 18 patients who completed treatment by October 2021 (candidemia $n = 12$, urinary tract infection (UTI) $n = 5$, intra-abdominal infection $n = 1$) revealed encouraging results with good outcomes. 72 % exhibited a complete or partial response, 11 % had stable disease, and only one patient with candidemia passed away due to unrelated causes. Other patients' outcomes were indeterminate. Notably, no side effects other than mild gastrointestinal symptoms were reported (Siebert et al., 2022). Remarkably, despite IBX's high protein-binding resulting in low concentration in the urine, the latest data presented at ECCMID's 33rd congress in 2023, focusing on 5 patients with *C. auris* UTI showed a 100 % complete or partial response to IBX (Siebert et al., 2023). This highlights the potential of IBX in treating UTI caused by *C. auris,* where azoles and echinocandins play a limited role.

Patients with IC constitute a significant proportion of the study population in the FURI trial, an ongoing, phase 3, multicenter, open-label single-arm study assessing the efficacy and safety of IBX in treating fungal diseases in patients who are either intolerant or refractory to SOC treatment (ClinicalTrials.gov, 2017b). The initial preliminary results were presented at the ECCMID's 29th congress, where an independent DRC evaluated the treatment response of 20 patients from 14 centers across 4 countries who completed therapy. These patients had a spectrum of infections ranging from mucocutaneous candidiasis to candidemia, endocarditis, and others. Among these patients, 55 % achieved a complete response, 30 % maintained stable disease, and 10 % had progressive disease. Notably, 8 patients had non-*albicans Candida* spp. These results provided an early indication of IBX's capability to effectively treat multiple infection sites caused by various *Candida* spp. (Cornely et al., 2019). These positive outcomes were reaffirmed in subsequent preliminary results presented at ECCMID's 31st congress. An interim analysis by an independent DRC, involving 33 patients from 14 centers in the United Kingdom, USA, and countries from the European Union, demonstrated that 70 % experienced clinical improvement, complete or partial response, and 21 % maintained a stable disease with no reported deaths. This analysis included patients with mucocutaneous candidiasis ($n = 9$), IC ($n = 15$), and IPA ($n = 3$). Multiple non-*albicans* species were detected, underscoring IBX's efficacy against a range of *Candida* spp. The most common treatment-related adverse events were mild to moderate diarrhea, nausea, and vomiting (Cornely et al., 2021). Additionally, the FURI trial has recently expanded its recruitment to include patients with endemic mycoses, although the results of this expansion are yet to be published (ClinicalTrials.gov, 2017b).

While the data on the efficacy and safety of IBX in managing IC are encouraging, the aforementioned trials have limitations. A larger sample size and investigations across various infection sites are required for a better assessment of the drug.

5.3. Invasive pulmonary aspergillosis

Aspergillus spp. are ubiquitous molds that are of specific threat to immunocompromised patients, those with structural lung disease (Kosmidis and Denning, 2015), and those following viral respiratory infections such as COVID-19 (Albrich and Lamoth, 2023). Despite their relatively low prevalence (Thompson and Young, 2021), they are associated with a high mortality rate (Tong et al., 2021), particularly as some species exhibit resistance to first-line antifungal agents (Resendiz Sharpe et al., 2018). Given IBX's robust in vitro activity against *Aspergillus* spp. (Ghannoum et al., 2018), there is an ongoing exploration of its potential as a treatment for patients with IPA in two different studies (ClinicalTrials.gov, 2019b, 2017b). The SCYNERGIA trial, a phase 2,

multicenter, randomized, double-blind clinic trial, is evaluating IBX's efficacy and tolerability in combination with voriconazole compared to voriconazole alone in patients diagnosed with IPA. The trial completed recruitment in March 2023, and its results are currently under review (ClinicalTrials.gov, 2019b). Furthermore, IPA is one of the conditions that are being examined by the FURI trial. For instance, in a recent preliminary analysis conducted by an independent DRC assessing the treatment response of 113 enrolled patients, 10 individuals (9.7 %) had IPA. Among them, 40 % exhibited complete, partial response or clinical improvement, 10 % had stable disease, and 40 % experienced disease progression (Thompson et al., 2022).

5.4. Real-world experience

Real-world data on the use of IBX is currently limited. The only published data so far comes from Vilnius University Hospital Santaros Klinikos, where Darasekvicius et al., reported in 2022 on 4 patients with hematologic malignancy who received IBX as salvage therapy (Daraskevicius et al., 2022). Three of the patients were infected with *P. kudriazvcevii* at multiple sites (1 UTI, 1 candidemia, 1 septic arthritis). The first 2 patients received IBX as monotherapy, while the patient with septic arthritis received IBX as part of combination therapy with LAMB. All 3 cases demonstrated clinical improvement, with a significant decrease in inflammatory markers, and no severe adverse events were reported. The fourth patient was treated with IBX in combination with LAMB and inhaled voriconazole for confirmed IPA. This treatment resulted in negative bronchoalveolar lavage results and a decrease in C-reactive protein. While these cases provide some insights into the real-world use of IBX, further evidence is needed to better understand IBX's efficacy and safety in diverse clinical scenarios.

6. Current place in treatment and future considerations

Although IBX shows promise as an antifungal agent for treating various IFI at multiple infection sites, as demonstrated in both clinical trials and real-world data so far, more studies are required to fully elucidate this agent's position among other lines in the treatment of different fungal infections. Along with other new antifungal agents in the pipeline, this drug could prove invaluable, especially given the rise of fungal resistance to azoles and echinocandins (Lockhart et al., 2023). Of particular concern is *C. auris*, a multi-drug resistant *Candida* spp. that is becoming increasingly prevalent (Pallotta et al., 2023), with the recent COVID-19 pandemic further exacerbating the problem (CDC, 2022b). The upcoming results from the CARES trial on IBX's efficacy in treating IFI secondary to *C. auris* are anticipated to determine whether IBX could represent a breakthrough in treatment. IBX's broad activity combined with its high bioavailability, positions it as an excellent candidate in various scenarios such as prophylaxis against IFI in immunocompromised patients, in addition to its use in combination therapy given its minimal interaction with other medications. Studies for these indications remain to be done. In addition, human data on IBX's efficacy and safety in the treatment of infections due to endemic mycoses as well as species causing mucormycosis (*Rhizopus* spp. *Mucor* spp.) are yet to be published. Although the use of this new oral antifungal agent could considerably lower the cost of care compared to using other intravenous antifungal agents such as echinocandins, the consideration of IBX's future application must also account for the possibility of the emergence of resistance and necessitates rigorous early monitoring as well as the implementation of vigilant regulation and stewardship measures (Kanj et al., 2023).

Currently, its FDA approval is specifically for the treatment of acute VVC (SCYNEXIS, 2021) as of June 2021 based on the results of the DOVE trial. In addition, in December 2022, it received approval as a treatment for recurrent VVC following the positive outcomes from the CANDLE trial. In fact, this makes IBX the first drug approved for the treatment of recurrent VVC (OB/GYN, 2022). As of now, it has not been FDA-approved for other indications and it has yet to be included in the guidelines of international medical societies for the treatment of various fungal diseases.

On November 12, 2021, this medication was granted orphan drug status in the European Union for addressing IC, entitling the developer to scientific and regulatory assistance from the European Medicines Agency (EMA) for progressing the medicine toward the stage of seeking marketing authorization (EMA, 2021).

7. Conclusion

In conclusion, IBX represents a first-in-class antifungal agent with a mechanism of action similar to echinocandins but with different binding sites, minimizing cross-resistance and rendering it effective against echinocandin-resistant isolates. Its broad spectrum of activity, efficacy against multi-drug and pan-resistant isolates, good oral bioavailability, minimal drug-drug interactions, and favorable safety profile position IBX as a potentially promising antifungal drug for treating invasive fungal disease caused by *Candida* spp, and *Aspergillus* spp. at multiple sites. Early results from clinical trials support its potential role in the future. It is currently FDA-approved for the treatment of acute VVC as well as for preventing its recurrence. Besides its efficacy, the oral administration of IBX may contribute to reducing healthcare costs associated with hospital length of stay and reducing the risk of hospital-acquired infections. However, certain aspects remain to be addressed. The safety of administering IBX in pediatric age groups and pregnant women is yet to be determined, and its efficacy in immunocompromised hosts requires further exploration. Additionally, its activity in patients infected with endemic mycoses has yet to be studied. Ongoing and additional clinical trials will contribute to a more comprehensive understanding of IBX's activity and safety in diverse patient populations and clinical scenarios.

Credit author statement

All authors contributed equally in the conceptualization and visualization of this review article. FA and EM contributed equally to the writing of the manuscript. LWA, FA, EM and SSK were all involved in the reviewing and editing of this review article. This review article was supervised by SSK as corresponding author.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

No acknowledgment.

References

Achkar, J.M., Fries, B.C., 2010. *Candida* infections of the genitourinary tract. Clin. Microbiol. Rev. 23, 253–273.

Ahmad, S., Alfouzan, W., 2021. *Candida auris*: epidemiology, diagnosis, pathogenesis, antifungal susceptibility, and infection control measures to combat the spread of infections in healthcare facilities. Microorganisms 9, 807.

Albrich, W.C., Lamoth, F., 2023. Viral-associated pulmonary aspergillosis: have we finally overcome the debate of colonization versus infection? Am. J. Respir. Crit. Care Med. 208, 230–231.

Aldejohann, A.M., Menner, C., Thielemann, N., Martin, R., Walther, G., Kurzai, O., 2024. In vitro activity of ibrexafungerp against clinically relevant echinocandin-resistant *Candida* strains. Antimicrob. Agents Chemother. 68, e0132423.

Alexander, B.D., Cornely, O., Pappas, P., Miller, R., Vazquez, J.A., Ostrosky-Zeichner, L., Spec, A., Rautemaa-Richardson, R., Krause, R., Thompson III, G.R., et al., 2020. Efficacy and safety of oral ibrexafungerp in 41 patients with refractory fungal diseases, interim analysis of a phase 3 open-label study (FURI). Open Forum Infect. Dis. 7, S642.

Alexander, B.D., Johnson, M.D., Pfeiffer, C.D., Jimenez-Ortigosa, C., Catania, J., Booker, R., Castanheira, M., Messer, S.A., Perlin, D.S., Pfaller, M.A., 2013. Increasing echinocandin resistance in *Candida glabrata*: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. Clin. Infect. Dis. 56, 1724–1732.

Angulo, D.A., Alexander, B., Rautemaa-Richardson, R., Alastruey-Izquierdo, A., Hoenigl, M., Ibrahim, A.S., Ghannoum, M.A., King, T.R., Azie, N.E., Walsh, T.J., 2022. Ibrexafungerp, a novel triterpenoid antifungal in development for the treatment of mold infections. J. Fungi (Basel) 8, 1121.

Apgar, J.M., Wilkening, R.R., Parker Jr., D.L., Meng, D., Wildonger, K.J., Sperbeck, D., Greenlee, M.L., Balkovec, J.M., Flattery, A.M., Abruzzo, G.K., Galgoci, A.M., Giacobbe, R.A., Gill, C.J., Hsu, M.J., Liberator, P., Misura, A.S., Motyl, M., Nielsen Kahn, J., Powles, M., Racine, F., Dragovic, J., Fan, W., Kirwan, R., Lee, S., Liu, H., Mamai, A., Nelson, K., Peel, M., 2021. Ibrexafungerp: an orally active beta-1,3-glucan synthesis inhibitor. Bioorg. Med. Chem. Lett. 32, 127661.

Arendrup, M.C., Jorgensen, K.M., Hare, R.K., Chowdhary, A., 2020. 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. Antimicrob. Agents Chemother. 64, e02136-19.

Astvad, K.M.T., Johansen, H.K., Roder, B.L., Rosenvinge, F.S., Knudsen, J.D., Lemming, L., Schonheyder, H.C., Hare, R.K., Kristensen, L., Nielsen, L., Gertsen, J.B., Dzajic, E., Pedersen, M., Ostergard, C., Olesen, B., Sondergaard, T.S., Arendrup, M. C., 2018. Update from a 12-year nationwide Fungemia surveillance: increasing intrinsic and acquired resistance causes concern. J. Clin. Microbiol. 56, e01564-17.

Barat, S.A., Borroto-Esoda, K., Angulo, D.A., Ashbaugh, A., Cushion, M., 2019. Efficacy of ibrexafungerp (formerly SCY-078) against *pneumocystis pneumonia* in a murine therapeutic model. In: European Congress of Clinical Microbiology and Infectious Diseases. Amsterdam, Netherlands.

Benedict, K., Jackson, B.R., Chiller, T., Beer, K.D., 2019. Estimation of direct healthcare costs of fungal diseases in the United States. Clin. Infect. Dis. 68, 1791–1797.

Berkow, E.L., Angulo, D., Lockhart, S.R., 2017. In vitro activity of a novel glucan synthase inhibitor, SCY-078, against clinical isolates of *Candida auris*. Antimicrob. Agents Chemother. 61, e00435-17.

Bongomin, F., Gago, S., Oladele, R.O., Denning, D.W., 2017. Global and multi-national prevalence of fungal diseases-estimate precision. J. Fungi (Basel) 3, 57.

Borroto-Esoda, K., Azie, N., Ashbaugh, A., Cushion, M., Angulo, D.A., 2020. Prevention of pneumocystis pneumonia by ibrexafungerp in a murine prophylaxis model. Open Forum Infect. Dis. 7, S643.

Borroto-Esoda, K., Barat, S., Angulo, D., Holden, K., Warn, P., 2017. SCY-078 demonstrates significant antifungal activity in a murine model of invasive aspergillosis. Open Forum Infect. Dis. 4, S472.

Casadevall, A., Kontoyiannis, D.P., Robert, V., 2019. On the emergence of *Candida auris*: climate change, azoles, swamps, and birds. mBio 10, e01397-19.

CDC. 2022a. 'Learn more about vaginal candidiasis (vaginal yeast infections', Accessed November 10 2023. https://www.cdc.gov/fungal/diseases/candidiasis/genital/index.html.

CDC. 2022b. 'COVID-19 U.S. IMPACT ON ANTIMICROBIAL RESISTANCE'. Accessed April 1 2024. https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf.

Chen, S.C., Slavin, M.A., Sorrell, T.C., 2011. Echinocandin antifungal drugs in fungal infections: a comparison. Drugs 71, 11–41.

Chowdhary, A., Sharma, C., Meis, J.F., 2017. *Candida auris*: a rapidly emerging cause of hospital-acquired multidrug-resistant fungal infections globally. PLoS. Pathog. 13, e1006290.

ClinicalTrials.gov. 2017a. 'Open-Label Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY-078) in Patients With Candidiasis Caused by *Candida auris* (CARES) (CARES)', Accessed November 10 2023. https://clinicaltrials.gov/study/NCT03363841.

ClinicalTrials.gov. 2017b. 'Study to Evaluate the Efficacy and Safety of Ibrexafungerp in Patients With Fungal Diseases That Are Refractory to or Intolerant of Standard Antifungal Treatment (FURI)', Accessed November 10 2023. https://clinicaltrials.gov/study/NCT03059992.

ClinicalTrials.gov. 2019a. 'Phase 3 Study of Oral Ibrexafungerp (SCY-078) Vs. Placebo in Subjects With Recurrent Vulvovaginal Candidiasis (VVC) (CANDLE)', Accessed November 10 2023. https://clinicaltrials.gov/study/NCT04029116.

ClinicalTrials.gov. 2019b. 'Study to Evaluate the Safety and Efficacy of the Coadministration of Ibrexafungerp (SCY-078) With Voriconazole in Patients With Invasive Pulmonary Aspergillosis (SCYNERGIA)', Accessed November 10 2023. https://clinicaltrials.gov/study/NCT03672292?intr=NCT03672292&rank=1.

ClinicalTrials.gov. 2022a. 'Ibrexafungerp for the Treatment of Complicated Vulvovaginal Candidiasis', Accessed November 10 2023. https://clinicaltrials.gov/study/NCT05399641.

ClinicalTrials.gov. 2022b. 'Phase 3, Randomized, Double-blind Study for Patients With Invasive Candidiasis Treated With IV Echinocandin Followed by Either Oral Ibrexafungerp or Oral Fluconazole (MARIO)', Accessed November 10 2023. https://clinicaltrials.gov/study/NCT05178862.

ClinicalTrials.gov. 2023. 'Safety of Pregnant Subjects Exposed to Ibrexafungerp Including Infant Outcomes', Accessed April 1 2024. https://clinicaltrials.gov/study/NCT05908682.

Cornely, O.A., Koehler, P., Pappas, P.G., Mccarty, T., Miller, R., Vazquez, J., Sanders, J. W., Morse, C.G., Ostrosky-Zeichner, L., Krause, R., Prattes, J., Spec, A., Rautemaa-Richardson, R., Bazaz, R., Walsh, T.J., Marty, F.M., Gonzalez-Bocco, I.H., BD, A. lexander, Hoenigl, M., Miceli, M.H., Patterson, T.F., Azie, N.E., Angulo, D.A., 2021. Outcomes of oral ibrexafungerp in 33 patients with refractory fungal diseases, interim analysis of a phase III open-label study (FURI) 06. Fungal infection & disease. In: European Congress of Clinical Microbiology and Infectious Diseases. Vienna, Austria.

Cornely, O.A., Ostrosky-Zeichner, L., Miller, R., Spec, A., Thompson, G., Walsh, T.J., Richardson, R., Krause, R., Pappas, P.G., Mullane, K., Morse, C.G., Sanders, J.W., Weiss, G., Witzke, O., Vazquez, J., Miceli, M.H., Patterson, T., Hoenigl, M., Alexander, B., Gonzalez, D.A., 2019. Favorable response to oral ibrexafungerp (formerly SCY-078) in patients with refractory fungal diseases, interim analysis by pathogen from a phase 3 open-label study (FURI). In: European Congress of Clinical Microbiology and Infectious Diseases. Amsterdam, Netherlands.

Daraskevicius, J., Petraitis, V., Davainis, L., Zucenka, A., 2022. The feasibility of ibrexafungerp for the treatment of fungal infections in patients with hematological malignancies. J. Fungi (Basel) 8, 440.

Davis, M.R., Donnelley, M.A., Thompson, G.R., 2020. Ibrexafungerp: a novel oral glucan synthase inhibitor. Med. Mycol. 58, 579–592.

Denning, D.W., Kneale, M., Sobel, J.D., Rautemaa-Richardson, R., 2018. Global burden of recurrent vulvovaginal candidiasis: a systematic review. Lancet Infect. Dis. 18, e339–ee47.

EMA. 2021. 'EU/3/21/2525: orphan designation for the treatment of invasive candidiasis', Accessed November 10 2023. https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-21-2525.

FDA. 2021. 'BREXAFEMME® (ibrexafungerp tablets), for oral use', Accessed April 1 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214900s000lbl.pdf.

Falagas, M.E., Apostolou, K.E., Pappas, V.D., 2006. Attributable mortality of candidemia: a systematic review of matched cohort and case–control studies. Eur. J. Clin. Microbiol. Infect. Dis. 25, 419–425.

Garcia-Rubio, R., de Oliveira, H.C., Rivera, J., Trevijano-Contador, N., 2019. The fungal cell wall: *Candida*, Cryptococcus, and *Aspergillus* species. Front. Microbiol. 10, 2993.

Gebremariam, T., Alkhazraji, S., Gu, Y., Najvar, L., Wiederhold, N., Patterson, T., Filler, S., Ibrahim, A., 2022. Efficacy assessment of ibrexafungerp in the neutropenic mouse model of pulmonary mucormycosis. In: European Congress of Clinical Microbiology and Infectious Diseases. Lisbon, Portugal.

Ghannoum, M., Arendrup, M.C., Chaturvedi, V.P., Lockhart, S.R., McCormick, T.S., Chaturvedi, S., Berkow, E.L., Juneja, D., Tarai, B., Azie, N., Angulo, D., Walsh, T.J., 2020a. Ibrexafungerp: a novel oral triterpenoid antifungal in development for the treatment of *Candida auris* infections. Antibiotics. (Basel) 9, 539.

Ghannoum, M., Isham, N., Angulo, D., Borroto-Esoda, K., Barat, S., Long, L., 2020b. Efficacy of ibrexafungerp (SCY-078) against *Candida auris* in an in vivo guinea pig cutaneous infection model. Antimicrob. Agents Chemother. 64, e00854-20.

Ghannoum, M., Long, L., Larkin, E.L., Isham, N., Sherif, R., Borroto-Esoda, K., Barat, S., Angulo, D., 2018. Evaluation of the antifungal activity of the novel oral glucan synthase inhibitor SCY-078, singly and in combination, for the treatment of invasive aspergillosis. Antimicrob. Agents Chemother. 62, e00244-18.

Goje, O., Sobel, R., Nyirjesy, P., Goldstein, S.R., Spitzer, M., Faught, B., Larson, S., King, T., Azie, N.E., Angulo, D., Sobel, J.D., 2023. Oral ibrexafungerp for vulvovaginal candidiasis treatment: an analysis of VANISH 303 and VANISH 306. J. Womens Health (Larchmt) 32, 178–186.

Hoenigl, M., Sprute, R., Egger, M., Arastehfar, A., Cornely, O.A., Krause, R., Lass-Flörl, C., Prattes, J., Spec, A., Thompson 3rd, G.R., Wiederhold, N., Jenks, J.D., 2021. The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. Drugs 8, 1703–1729.

Jallow, S., Govender, N.P., 2021. Ibrexafungerp: a first-in-class oral triterpenoid glucan synthase inhibitor. J. Fungi (Basel) 7.

Jimenez-Ortigosa, C., Paderu, P., Motyl, M.R., Perlin, D.S., 2014. Enfumafungin derivative MK-3118 shows increased in vitro potency against clinical echinocandin-resistant *Candida* species and *Aspergillus* species isolates. Antimicrob. Agents Chemother. 58, 1248–1251.

Jimenez-Ortigosa, C., Perez, W.B., Angulo, D., Borroto-Esoda, K., Perlin, D.S., 2017. De novo acquisition of resistance to SCY-078 in *Candida glabrata* involves FKS mutations that both overlap and are distinct from those conferring echinocandin resistance. Antimicrob. Agents Chemother. 61, e00833-17.

Juneja, D., Ross, C., Breedt, J., Siebert, R.S., Azie, N.E., Angulo, D.A., 2021. Outcomes of oral ibrexafungerp in the treatment of ten patients with *Candida auris* infections, from the CARES Study. In: European Congress of Clinical Microbiology and Infectious Disease. Vienna, Austria.

Kanj, S.S., Haddad, S.F., Meis, J.F., Verweij, P.E., Voss, A., Rautemaa-Richardson, R., Levy-Hara, G., Chowdhary, A., Ghafur, A., Brüggemann, R., Bal, A.M., Schouten, J., 2023. The battle against fungi: lessons in antifungal stewardship from COVID-19 times. Int. J. Antimicrob. Agents 62, 106846.

Kmeid, J., Jabbour, J.F., Kanj, S.S., 2020. Epidemiology and burden of invasive fungal infections in the countries of the Arab League. J. Infect. Public Health 13, 2080–2086.

Kordalewska, M., Lee, A., Park, S., Berrio, I., Chowdhary, A., Zhao, Y., Perlin, D.S., 2018. Understanding echinocandin resistance in the emerging pathogen *Candida auris*. Antimicrob. Agents Chemother. 62, e00238-18.

Kosmidis, C., Denning, D.W., 2015. The clinical spectrum of pulmonary aspergillosis. Thorax. 70, 270–277.

Lamoth, F., Alexander, B.D., 2015. Antifungal activities of SCY-078 (MK-3118) and standard antifungal agents against clinical non-*Aspergillus* mold isolates. Antimicrob. Agents Chemother. 59, 4308–4311.
Larkin, E., Hager, C., Chandra, J., Mukherjee, P.K., Retuerto, M., Salem, I., Long, L., Isham, N., Kovanda, L., Borroto-Esoda, K., Wring, S., Angulo, D., Ghannoum, M., 2017. The emerging pathogen *Candida auris*: growth phenotype, virulence factors, activity of antifungals, and effect of SCY-078, a novel glucan synthesis inhibitor, on growth morphology and biofilm formation. Antimicrob. Agents Chemother. 61, e02396-16.
Lee, A., Prideaux, B., Zimmerman, M., Carter, C., Barat, S., Angulo, D., Dartois, V., Perlin, D.S., Zhao, Y., 2020. Penetration of ibrexafungerp (formerly SCY-078) at the site of infection in an intra-abdominal candidiasis mouse model. Antimicrob. Agents Chemother. 64, e02268-19.
Lepak, A.J., Marchillo, K., Andes, D.R., 2015. Pharmacodynamic target evaluation of a novel oral glucan synthase inhibitor, SCY-078 (MK-3118), using an in vivo murine invasive candidiasis model. Antimicrob. Agents Chemother 59, 1265–1272.
Lockhart, S.R., Chowdhary, A., Gold, J.A.W., 2023. The rapid emergence of antifungal-resistant human-pathogenic fungi. Nat. Rev. Microbiol. 21, 818–832.
Long, L., Gowen, R., Angulo, D., Azie, N., Ghannoum, M.A., 2023. Evaluate the effect of ibrexafungerp alone and in combination with amphotericin B or posaconazole against Mucor strains using time-kill kinetics and scanning electron microscopy. In: European Congress of Clinical Microbiology and Infectious Diseases. Copenhagen, Denmark.
Marcos-Zambrano, L.J., Gomez-Perosanz, M., Escribano, P., Bouza, E., Guinea, J., 2017. The novel oral glucan synthase inhibitor SCY-078 shows in vitro activity against sessile and planktonic *Candida* spp. J. Antimicrob. Chemother. 72, 1969–1976.
Mesquida, A., Diaz-Garcia, J., Sanchez-Carrillo, C., Martin-Rabadan, P., Alcala, L., Munoz, P., Escribano, P., Guinea, J., 2022. DeltaF659 and F659S substitutions at the HS1 of FKS2 gene, along with E655A and W715L upstream and downstream substitutions, correlate with high ibrexafungerp MICs against *Candida glabrata*. Clin. Microbiol. Infect. 28, 1154.e5–1154.e8.
Murphy, G., Hyman, M., Willett, M., Angulo, D., 2017. CYP-mediated drug interaction profile of SCY-078, a novel glucan synthase inhibitor (GSI). In: ASM Microbe. New Orleans, Louisiana, USA.
Naicker, S.D., Magobo, R.E., Zulu, T.G., Maphanga, T.G., Luthuli, N., Lowman, W., Govender, N.P., 2016. Two echinocandin-resistant *Candida glabrata* FKS mutants from South Africa. Med. Mycol. Case Rep. 11, 24–26.
Nunnally, N.S., Etienne, K.A., Angulo, D., Lockhart, S.R., Berkow, E.L., 2019. In vitro activity of ibrexafungerp, a novel glucan synthase inhibitor against *Candida glabrata* isolates with FKS mutations. Antimicrob. Agents Chemother. 63, e01692-19.
Nyirjesy, P., Brookhart, C., Lazenby, G., Schwebke, J., Sobel, J.D., 2022a. Vulvovaginal candidiasis: a review of the evidence for the 2021 centers for disease control and prevention of sexually transmitted infections treatment guidelines. Clin. Infect. Dis. 74, S162–SS68.
Nyirjesy, P., Schwebke, J.R., Angulo, D.A., Harriott, I.A., Azie, N.E., Sobel, J.D., 2022b. Phase 2 randomized study of oral ibrexafungerp versus fluconazole in vulvovaginal candidiasis. Clin. Infect. Dis. 74, 2129–2135.
OB/GYN, Contemporary. 2022. 'FDA approves ibrexafungerp for reduction in the incidence of RVVC'. https://www.contemporaryobgyn.net/view/fda-approves-ibrexafungerp-for-reduction-in-the-incidence-of-rvvc.
Odds, F.C., Brown, A.J., Gow, N.A., 2003. Antifungal agents: mechanisms of action. Trends Microbiol. 11, 272–279.
Pallotta, F., Viale, P., Barchiesi, F., 2023. *Candida auris*: the new fungal threat. Infez. Med. 31, 323–328.
Pappas, P.G., Kauffman, C.A., Andes, D.R., Clancy, C.J., Marr, K.A., Ostrosky-Zeichner, L., Reboli, A.C., Schuster, M.G., Vazquez, J.A., Walsh, T.J., Zaoutis, T.E., Sobel, J.D., 2016. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. Clin. Infect. Dis. 62, e1–50.
Perlin, D.S., 2007. Resistance to echinocandin-class antifungal drugs. Drug Resist. Updat. 10, 121–130.
Petraitis, V., Petraitiene, R., Katragkou, A., Maung, B.B.W., Naing, E., Kavaliauskas, P., Barat, S., Borroto-Esoda, K., Azie, N., Angulo, D., Walsh, T.J., 2020. Combination therapy with ibrexafungerp (formerly SCY-078), a first-in-class triterpenoid inhibitor of (1–>3)-beta-d-glucan synthesis, and isavuconazole for treatment of experimental invasive pulmonary aspergillosis. Antimicrob. Agents Chemother. 64, e02429-19.
Pfaller, M.A., Messer, S.A., Motyl, M.R., Jones, R.N., Castanheira, M., 2013. In vitro activity of a new oral glucan synthase inhibitor (MK-3118) tested against *Aspergillus* spp. by CLSI and EUCAST broth microdilution methods. Antimicrob. Agents Chemother. 57, 1065–1068.
Pfaller, M.A., Messer, S.A., Rhomberg, P.R., Borroto-Esoda, K., Castanheira, M., 2017. Differential activity of the oral glucan synthase inhibitor SCY-078 against wild-type and echinocandin-resistant strains of *Candida* species. Antimicrob. Agents Chemother 61, e00161-17.
Porollo, A., Meller, J., Joshi, Y., Jaiswal, V., Smulian, A.G., Cushion, M.T., 2012. Analysis of current antifungal agents and their targets within the *Pneumocystis carinii* genome. Curr. Drug Targets 13, 1575–1585.
Quindos, G., Miranda-Cadena, K., San-Millan, R., Borroto-Esoda, K., Canton, E., Linares-Sicilia, M.J., Hamprecht, A., Montesinos, I., Tortorano, A.M., Prigitano, A., Vidal-Garcia, M., Marcos-Arias, C., Guridi, A., Sanchez-Reus, F., Machuca-Barcena, J., Rodriguez-Iglesias, M.A., Martin-Mazuelos, E., Castro-Mendez, C., Lopez-Soria, L., Ruiz-Gaitan, A., Fernandez-Rivero, M., Lorenzo, D., Capilla, J., Rezusta, A., Peman, J., Guarro, J., Pereira, J., Pais, C., Romeo, O., Ezpeleta, G., Jauregizar, N., Angulo, D., Eraso, E., 2022. In vitro antifungal activity of ibrexafungerp (SCY-078) against contemporary blood isolates from medically relevant species of *Candida*: a European study. Front. Cell Infect. Microbiol. 12, 906563.
Resendiz Sharpe, A., Lagrou, K., Meis, J.F., Chowdhary, A., Lockhart, S.R., Verweij, P.E., Isham Ecmm Aspergillus Resistance Surveillance Working Group, 2018. Triazole resistance surveillance in *Aspergillus* fumigatus. Med. Mycol. 56, 83–92.
Rivero-Menendez, O., Soto-Debran, J.C., Cuenca-Estrella, M., Alastruey-Izquierdo, A., 2021. In vitro activity of ibrexafungerp against a collection of clinical isolates of *Aspergillus*, including cryptic species and Cyp51A mutants, using EUCAST and CLSI methodologies. J. Fungi (Basel) 7, 232.
Rocha, E.M., Garcia-Effron, G., Park, S., Perlin, D.S., 2007. A Ser678Pro substitution in Fks1p confers resistance to echinocandin drugs in *Aspergillus* fumigatus. Antimicrob. Agents Chemother. 51, 4174–4176.
Schell, W.A., Jones, A.M., Borroto-Esoda, K., Alexander, B.D., 2017. Antifungal activity of SCY-078 and standard antifungal agents against 178 clinical isolates of resistant and susceptible *Candida* species. Antimicrob. Agents Chemother. 61, e01102-17.
Schwebke, J.R., Sobel, R., Gersten, J.K., Sussman, S.A., Lederman, S.N., Jacobs, M.A., Chappell, B.T., Weinstein, D.L., Moffett, A.H., Azie, N.E., Angulo, D.A., Harriott, I.A., Borroto-Esoda, K., Ghannoum, M.A., Nyirjesy, P., Sobel, J.D., 2022. Ibrexafungerp versus placebo for vulvovaginal candidiasis treatment: a phase 3, randomized, controlled superiority trial (VANISH 303). Clin. Infect. Dis. 74, 1979–1985.
Scorneaux, B., Angulo, D., Borroto-Esoda, K., Ghannoum, M., Peel, M., Wring, S., 2017. SCY-078 is fungicidal against *Candida* species in time-kill studies. Antimicrob. Agents Chemother. 61, e01961-16.
SCYNEXIS, Inc. 2021. 'SCYNEXIS announces FDA approval of BREXAFEMME R (ibrexafungerp tablets) as the first and only oral non-azole treatment for vaginal yeast infections [media release].', Accessed November 10 2023. https://www.biospace.com/article/releases/scynexis-announces-fda-approval-of-brexafemme-ibrexafungerp-tablets-as-the-first-and-only-oral-non-azole-treatment-for-vaginal-yeast-infections/.
Seagle, E.E., Williams, S.L., Chiller, T.M., 2021. Recent trends in the epidemiology of fungal infections. Infect. Dis. Clin. North Am. 35, 237–260.
Seiler, G.T., Ostrosky-Zeichner, L., 2021. Investigational agents for the treatment of resistant yeasts and molds. Curr. Fungal Infect. Rep. 15, 104–115.
Seyedmousavi, S., Mouton, J.W., Melchers, W.J., Bruggemann, R.J., Verweij, P.E., 2014. The role of azoles in the management of azole-resistant aspergillosis: from the bench to the bedside. Drug Resist. Updat. 17, 37–50.
Siebert, R.S., Juneja, D., Nguyen, M.H., Vazquez, J., Azie, N.E., Angulo, D.A., 2023. Outcomes of oral ibrexafungerp in subjects with urinary tract infections from two phase 3 openlabel studies: difficult-to-treat invasive fungal infections (FURI) and infections with *Candida auris* (CARES). In: European Congress of Clinical Microbiology and Infectious Diseases. Copenhagen, Denmark.
Siebert, R.S., Juneja, D., Singh, O., Tarai, B., Ross, C., Reuben, R.C., Breedt, J., Yaddanapudi, N., Conradie, M., Mahmood, F., Sanchez, S., King, T.R., Azie, N.E., Angulo, D.A., 2022. Outcomes of oral ibrexafungerp in the treatment of 18 patients with *Candida auris* infections, from the CARES study. In: European Congress of Clinical Microbiology and Infectious Diseases. Lisbon, Portugal.
Snelders, E., Huis In 't Veld, R.A., Rijs, A.J., Kema, G.H., Melchers, W.J., Verweij, P.E., 2009. Possible environmental origin of resistance of *Aspergillus* fumigatus to medical triazoles. Appl. Environ. Microbiol. 75, 4053–4057.
Sobel, J.D., 2007. Vulvovaginal candidosis. Lancet 369, 1961–1971.
Sobel, R., Nyirjesy, P., Ghannoum, M.A., Delchev, D.A., Azie, N.E., Angulo, D., Harriott, I.A., Borroto-Esoda, K., Sobel, J.D., 2022. Efficacy and safety of oral ibrexafungerp for the treatment of acute vulvovaginal candidiasis: a global phase 3, randomised, placebo-controlled superiority study (VANISH 306). BJOG. 129, 412–420.
Spec, A., Pullman, J., Thompson, G.R., Powderly, W.G., Tobin, E.H., Vazquez, J., Wring, S.A., Angulo, D., Helou, S., Pappas, P.G., Study, G.roup M.ycoses, 2019. MSG-10: a Phase 2 study of oral ibrexafungerp (SCY-078) following initial echinocandin therapy in non-neutropenic patients with invasive candidiasis. J. Antimicrob. Chemother 74, 3056–3062.
Thompson, G.R., King, T., Azie, N., Angulo, D.A., Prattes, J., 2022. Oral ibrexafungerp outcomes by fungal disease in patients from an interim analysis of a phase 3 open-label study (FURI). Open Forum Infect. Dis. 9, ofac492.064.
Thompson 3rd, G.R., Young, J.H., 2021. *Aspergillus* infections. N. Engl. J. Med. 385, 1496–1509.
Tong, X., Liu, T., Jiang, K., Wang, D., Liu, S., Wang, Y., Fan, H., 2021. Clinical characteristics and prognostic risk factors of patients with proven invasive pulmonary aspergillosis: a single-institution retrospective study. Front. Med. (Lausanne) 8, 756237.
Trucksis, M., Garrett, G., Bautmans, A., et al., 2011. A phase I multiple rising dose study evaluating safety, tolerability, and pharmacokinetics of MK-3118, oral glucan synthase inhibitor, in healthy volunteers. In: 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Chicago, Illinois, USA.
Trucksis, M., Garrett, G., Heirman, I., et al., 2010. A phase I single rising dose study evaluating the safety, tolerability and pharmacokinetics of an oral glucan synthase inhibitor in healthy male volunteers. In: 50th Interscience Conference on Antimicrobial Agents and Chemotherapy. Boston, Massachusetts, USA.
Verweij, P.E., Snelders, E., Kema, G.H., Mellado, E., Melchers, W.J., 2009. Azole resistance in *Aspergillus* fumigatus: a side-effect of environmental fungicide use? Lancet Infect. Dis. 9, 789–795.
Walker, S.S., Xu, Y., Triantafyllou, I., Waldman, M.F., Mendrick, C., Brown, N., Mann, P., Chau, A., Patel, R., Bauman, N., Norris, C., Antonacci, B., Gurnani, M., Cacciapuoti, A., McNicholas, P.M., Wainhaus, S., Herr, R.J., Kuang, R., Aslanian, R. G., Ting, P.C., Black, T.A., 2011. Discovery of a novel class of orally active antifungal beta-1,3-D-glucan synthase inhibitors. Antimicrob. Agents Chemother. 55, 5099–5106.
Wiederhold, N.P., 2021. Emerging fungal infections: new species, new names, and antifungal resistance. Clin. Chem. 68, 83–90.

Wiederhold, N.P., 2022. Pharmacodynamics, mechanisms of action and resistance, and spectrum of activity of new antifungal agents. J. Fungi (Basel) 8, 857.
Wiederhold, N.P., Najvar, L.K., Jaramillo, R., Olivo, M., Pizzini, J., Catano, G., Patterson, T.F., 2018. Oral glucan synthase inhibitor SCY-078 is effective in an experimental murine model of invasive candidiasis caused by WT and echinocandin-resistant *Candida glabrata*. J. Antimicrob. Chemother. 73, 448–451.
Wisplinghoff, H., Bischoff, T., Tallent, S.M., Seifert, H., Wenzel, R.P., Edmond, M.B., 2004. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin. Infect. Dis. 39, 309–317.
World Health Organization. 2022. 'WHO releases first-ever list of health-threatening fungi', Accessed November 10 2023. https://www.who.int/news/item/25-10-2022-who-releases-first-ever-list-of-health-threatening-fungi.
Wring, S., Borroto-Esoda, K., Solon, E., Angulo, D., 2019a. SCY-078, a novel fungicidal agent, demonstrates distribution to tissues associated with fungal infections during mass balance studies with intravenous and oral [(14)C]SCY-078 in albino and pigmented rats. Antimicrob. Agents Chemother. 63, e02119-18.
Wring, S., Murphy, G., Atiee, G., Corr, C., Hyman, M., Willett, M., Angulo, D., 2018. Lack of impact by SCY-078, a first-in-class oral fungicidal glucan synthase inhibitor, on the pharmacokinetics of rosiglitazone, a substrate for CYP450 2C8, supports the low risk for clinically relevant metabolic drug-drug interactions. J. Clin. Pharmacol. 58, 1305–1313.
Wring, S., Murphy, G., Atiee, G., Corr, C., Hyman, M., Willett, M., Angulo, D., 2019b. Clinical pharmacokinetics and drug-drug interaction potential for coadministered SCY-078, an oral fungicidal glucan synthase inhibitor, and tacrolimus. Clin. Pharmacol. Drug Dev. 8, 60–69.
Wring, S.A., Randolph, R., Park, S., Abruzzo, G., Chen, Q., Flattery, A., Garrett, G., Peel, M., Outcalt, R., Powell, K., Trucksis, M., Angulo, D., Borroto-Esoda, K., 2017. Preclinical pharmacokinetics and pharmacodynamic target of SCY-078, a first-in-class orally active antifungal glucan synthesis inhibitor, in murine models of disseminated candidiasis. Antimicrob. Agents Chemother. 61, e02068-16.
Zhu, Y.C., Barat, S.A., Borroto-Esoda, K., Angulo, D., Chaturvedi, S., Chaturvedi, V., 2020. Pan-resistant *Candida auris* isolates from the outbreak in New York are susceptible to ibrexafungerp (a glucan synthase inhibitor). Int. J. Antimicrob. Agents 55, 105922.