

Ibexafungerp: a novel oral triterpenoid antifungal, as an emerging therapeutic option in Vulvovaginal Candidiasis (VVC)

D.S. Chakraborty¹, S. Choudhury², S. Lahiry³

¹Department of Pharmacology, Diamond Harbour Govt. Medical College, Diamond Harbour, India

²Department of Pharmacology, Burdwan Medical College, Burdwan, India

³Independent Research Scholar, Kolkata, India

ABSTRACT:

- **Objective:** Vulvovaginal candidiasis (VVC) is a major concern for women of reproductive age group affecting more than 70% of total population of the mentioned population. Apart from *Candida albicans* as a predominant etiological fungal agent, other non albican species as *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. parapsilosis*, *Trichosporon spp.*, *zygomycetes spp* and *Saccharomyces cerevisiae* have also proven to be other important agents causing the disease. The situation becomes difficult when the usual conventional therapeutic modalities like oral and local azoles, as well as boric acid and flucytosine fail to cure the disease and raise the burden of resistant strains.
- **Results:** Iberxafungerp, as a novel oral triterpenoid oral antifungal, has been evolved to treat VVC by interacting differently with the target cell unlike other echinocandins. Additionally, it has a broader antifungal spectrum, fungicidal activity against *Candida spp.*, high tissue penetration into target tissues, activity at low pH, and no preclinical fetal toxicity, which addresses many of the unmet needs of existing antifungal drugs for VVC.
- **Conclusions:** Available data obtained from recently completed clinical trials on safety and efficacy of this drug in treatment of VVC, as well as recent approval from FDA raise a great hope to treat the drug-resistant pathogens.
- **Keywords:** Vulvovaginal, Triterpenoid, Novel, Oral, Safety, Azole resistant.

INTRODUCTION

Vulvovaginal candidiasis (VVC) is a common infection of the lower female genital tract that primarily affects women of reproductive age who are immunocompetent. It is a condition that affects women of all races and socioeconomic backgrounds^{1,2}. According to currently avail-

able data, 70-75% of women will have VVC at least once in their lifetime³. *Candida albicans* is the most common species in 90-95% of cases, followed by non-albicans species such as *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. parapsilosis*⁴. *Trichosporon spp.*, *zygomycetes spp.*, and *Saccharomyces cerevisiae* are said to induce symptomatic vaginitis in rare anecdotal case reports. Accord-



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ing to epidemiological data, the whole female population's incidence ranges from 12-57%^{2,3}. Given that acute VVC is underreported to clinicians due to generally successful over-the-counter treatment alternatives, estimating the incidence rate is almost impossible⁵. *C. albicans*, a component of the typical human microbiota, colonize the vaginal lumen asymptotically⁶. However, profuse mucosal inflammation produced predominantly by fungal proliferation in the vagina and subsequent epithelial invasion and generation of virulence effectors might result in symptomatic infection. Candida-related infections, aside from asymptomatic fungal colonization, are the second biggest cause of vaginitis, mostly affecting women during their reproductive age, when high estrogen levels increase the glycogen content of the vaginal epithelium, hence providing food for the yeast⁷. Because 50% of women who have an infection will have a second episode, and 5-8% may develop recurrent vulvovaginal candidiasis (RVVC), it is critical to distinguish between colonization and infection. RVVC is defined as four or more episodes of VVC in a calendar year. According to recent research, roughly 138 million women are affected by RVVC each year, with an additional 372 million affected across their lifetimes. The majority of RVVC events occur between the ages of 19 and 35, with a prevalence rate of 9% by the age of 50, according to a survey⁴. According to Fidel et al⁸, women with RVVC have a problem with the normally protective immune response triggered by a previous *Candida* infection⁸⁻¹². The azoles' static activity and insufficient immune-mediated clearance are important factors in illness recurrence. Antibiotics, sexual activity, high-estrogen-containing oral contraceptives, pregnancy, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and uncontrolled diabetic mellitus are all risk factors for VVC^{13,14}. Although genome-wide association studies have begun to unravel certain genetic determinants of susceptibility, there are currently no identified risk factors for RVVC¹⁴.

MATERIALS AND METHODS

After an extensive literature search using the databases PubMed, Scopus and Cochrane it was found that Short-course therapy with topical or oral systemic azole medications works well for uncomplicated VVC. The path of therapy should be chosen and determined by the women. The majority prefer oral medication because it is more convenient; however, topical medicines may provide relief sooner. More complicated infections require a longer course of treatment, especially in severe cases and in compromised hosts (pregnancy, diabetes, etc.). Complicated VVC caused by non-albicans *Candida spp.* necessitates further care. While *C. tropicalis* infection is uncommon, it can be treated with conventional azoles if the treatment is not rushed. However, boric acid or flucytosine therapy is frequently required for *C. krusei* and, in particular, *C. glabrata*. Long-term maintenance suppressive therapy with oral once-weekly fluconazole is used to control complicated recurrent VVC, which requires attention to the underlying cause. Unfortunately,

while the recurrence rate is relatively low (about 7%) while on the well-tolerated fluconazole when prophylaxis is stopped, a substantial risk of recurrence might be expected¹⁵. There are no additional oral therapy choices for people who have vulvovaginal infections caused by an azole-resistant organism or who do not respond to fluconazole. Topical boric acid or nystatin suppositories compounded amphotericin B for topical use, or various systemic antifungals in severe cases are already available as alternatives^{16,17}.

When these fail, women are left with few options for treatment. Although itraconazole is licensed for the treatment of VVC in the EU, it is rarely utilized. Furthermore, systemic azoles like fluconazole, including the single oral 150 mg dose during pregnancy, carry the risk of fetal harm¹⁸. Oral azole antifungals, which are now used to treat both acute VVC and RVVC prevention, have limitations. Overexpression of efflux pumps, up-regulation of transporters, overexpression of drug targets, mutations, and mitochondrial abnormalities all contribute to azole resistance in *Candida spp.* identified in VVC¹⁹⁻²¹. New medicines must also have long-term efficacy to prevent recurrence in women with RVVC, as well as be safe and well-tolerated, especially when long-term therapy is required. High tissue penetration, particularly into vaginal tissues, and notable activity at a low pH, as well as low risk of drug-drug interactions, particularly with oral contraceptives, are further criteria of an optimal antifungal agent for treating VVC.

Ibrexafungerp (previously SCY-078) is a new, orally active triterpenoid antifungal that, like echinocandins, causes a decrease in (1,3)—D-glucan polymers and a weakening of the fungal cell wall²². In comparison to echinocandins, Ibrexafungerp, the first member of the 'fungerp' family of drugs, is a structurally unique triterpenoid glucan synthase inhibitor that interacts differently with the target cell²³. *In vitro*, Ibrexafungerp inhibits a wide spectrum of *Candida* isolates with *fks1* and *fks2* point mutations, which produce echinocandin resistance in *Candida glabrata*, *Candida auris*, and *Aspergillus spp.*²⁴⁻³³. The discovery of enfumafungin, a triterpene glycoside, came as a result of active research into new medications using high throughput screening of natural compounds from an endophytic fungus³⁴. Enfumafungin differs structurally from echinocandins, producing a novel antifungal class known as "fungerps" (Antifungal Triterpenoid)³⁴⁻³⁹. The semi-synthetic derivative Ibrexafungerp was developed after enfumafungin was modified for enhanced oral absorption and pharmacokinetic characteristics (IBX)⁴⁰. Ibrexafungerp (IBX) works in a similar way to echinocandins, blocking the -(1,3) D-glucan synthase enzyme in a non-competitive manner^{41,42}. IBX, like echinocandins, displays fungicidal and fungistatic effects on *Candida spp.*²⁸ and *Aspergillus spp.*^{29,30}. The Ibrexafungerp and echinocandin-binding sites on the enzyme, on the other hand, are not identical but partially overlap, resulting in very limited cross-resistance across echinocandin- and Ibrexafungerp-resistant strains. Pharmacokinetic properties of Ibrexafungerp in comparison to other echinocandins are summarized in Table 1.

Table 1. Pharmacokinetic properties of Ibrexafungerp in comparison to other echinocandins⁴³.

| Variables | Ibrexafungerp | Anidulafungin | Caspofungin | Micafungin |
|-----------------------------------|-----------------------------------|---------------|-------------|------------|
| Oral Bio-availability | 35-51% | < 5% | < 5% | < 5% |
| Food Effect | High fat diet improves absorption | NA | NA | NA |
| Volume of Distribution (in Litre) | 4.7-5.3 | 0.43-0.71 | 0.14 | 0.39 |
| Protein Binding (%) | 99.6-99.8 | 84 | 97 | 99 |
| Half Life (in hrs) | 20-30 | 26 | 30 | 15 |
| Metabolism | Hepatic | None | Hepatic | Hepatic |
| Elimination | Feces | Feces | Urine | Feces |

DISCUSSION

Ibrexafungerp is a substrate of CYP3A4 and a possible inhibitor of cytochrome (CYP) 2C8, according to *in vitro* research^{44,45}. It has a low activity for other CYP isoenzymes. To assess the drug-drug interaction potential of Ibrexafungerp, four Phase 1 investigations were done in healthy participants⁴⁶. After single or several doses of Ibrexafungerp, studies looked at the interaction potential of ketoconazole and diltiazem (CYP3A4 inhibitors), rosiglitazone (CYP2C8 substrate), and tacrolimus (CYP3A4 substrate). Ibrexafungerp had no therapeutically relevant effect on 2C8 inhibition or 3A4 substrates. When combined with powerful CYP3A4 inhibitors, Ibrexafungerp may require a dosage change. Oral contraceptives are unlikely to interact with Ibrexafungerp. The proarrhythmic effect of Ibrexafungerp was assessed in healthy people in a thorough QT study to establish effects on heart rate and an exposure-response analysis⁴⁷. The effects of Ibrexafungerp on heart rate, PR, and QRS intervals were not clinically significant. After IV dosages of 125, 250, and 375 mg, no clinically relevant effect of Ibrexafungerp on the QTc-F interval was seen at plasma concentration ranges up to 4000 ng/mL. At therapeutic exposures, Ibrexafungerp has a low risk of CYP-mediated medication interactions. In a phase I trial, Ibrexafungerp and placebo had equal rates of non-serious side effects (AE), with 22/24 individuals in the treatment arm and 7/8 subjects in the placebo arm reporting AEs⁴⁸.

As previously established⁴⁹, Ibrexafungerp's higher activity in an acidic medium may be beneficial for treating *Candida spp.* vaginal infections. Susceptibility testing for *Candida albicans* and *Candida glabrata* isolates was done with Ibrexafungerp, micafungin, and fluconazole in a test medium adjusted to pH values of 7.0, 5.7, and 4.5. While *Candida albicans* is the most common causative pathogen of VVC, additional *Candida* species, such as *C. glabrata*, *C. parapsilosis*, *C. krusei*, and *C. tropicalis*, have been identified as pathogenic species in recent years⁵⁰. The frequency of non-albicans *Candida* (NAC) species as a cause of VVC has increased in recent years, with NAC species accounting for 10% to 45 percent of VVC infections⁵¹. Ibrexafungerp showed antifungal effectiveness against *C. glabrata*, *C. krusei*, *C. tropicalis*, and *C. parapsilosis*, all of which have reduced fluconazole susceptibility⁴³. Ibrexafungerp has been shown to have potent fungicidal action

against a variety of *Candida* species⁵². Ibrexafungerp showed fungicidal efficacy after 24 hours in a time-kill assay. Fluconazole and voriconazole, on the other hand, were fungistatic⁵³. Ibrexafungerp is active against a wide range of *Candida* species, including echinocandin- and azole-resistant isolates, as well as isolates with FKS1 or FKS2 mutations, *Aspergillus spp.*, and other fungal pathogens, *in vitro*. Ibrexafungerp regularly outperforms fluconazole *in vitro* against *Candida spp.*, notably among echinocandin- and azole-resistant isolates⁵⁴. FKS mutations in the glucan synthase gene cause resistance to Ibrexafungerp. Although this region largely overlaps with an echinocandin binding site, the binding site appears to be nonidentical, suggesting a decreased rate of Ibrexafungerp resistance⁵⁵. Ibrexafungerp activity was scarcely influenced by the presence of FKS mutations in a study evaluating its activity against wild-type and echinocandin-resistant *Candida spp.*⁴¹FKS1 (F625del) and FKS2 (F659del) deletion mutations result in 40-fold and >121-fold increases in the MIC₅₀ for Ibrexafungerp, respectively⁵⁶. The bulk of IBX resistance mutations in *C. glabrata* are found in the FKS2 gene, which supports the theory that the FKS2 gene is primarily involved in -(1,3) D-glucan production in *C. glabrata*⁵⁷.

In two Phase 2 studies, the safety and efficacy of Ibrexafungerp were assessed. One proof-of-concept study of women with moderate to severe VVC (clinicaltrials.gov: NCT02679456)⁵⁸. DOVE (clinicaltrials.gov: NCT03253094), a Phase 2 randomized, double-blind, active-controlled dose-finding study that enrolled women with moderate or severe acute VVC, was the second study⁵⁹. Both studies showed clinical results that were comparable to fluconazole. Ibrexafungerp was generally well tolerated. The majority of adverse events (AEs) were mild to severe and lasted for one day. The oral formulation of Ibrexafungerp has been the subject of the majority of clinical investigations⁶⁰. Six investigations on the efficacy of Ibrexafungerp for the treatment of vulvovaginal candidiasis (VVC) and the prevention of recurrence of VVC were conducted (Table 2).

These trials⁶¹⁻⁶³ indicated a satisfactory safety and tolerability profile, as well as high efficacy in the context of VVC, resulting in the US Food and Drug Administration (FDA) accepting a new drug application (NDA) for the treatment of VVC with Ibrexafungerp. The FDA also granted Ibrexafungerp Qualified Infectious Disease Product (QIDP) and Fast Track designations for the treatment of VVC and prevention of recurrent VVC⁶⁴.

Table 2. Summary of trials on Ibrexafungerp in vulvovaginal candidiasis.

| Phase of Trial | Trial identification number (NCT Number) | Title | Acronym (if any) | Sample size | Drugs used | Outcome Parameters | Study start date | Study completion date |
|----------------|--|--|------------------|-------------|---------------------------|---|-------------------|-----------------------|
| Phase 2 | NCT03253094 | An Active-Controlled, Dose-Finding Study of Oral IBX vs. Oral Fluconazole in Subjects With Acute Vulvovaginal Candidiasis | DOVE | 186 | Fluconazole and SCY-078 | Clinical cure (complete resolution of signs and symptoms) Co-occurrence of clinical and mycological cure | 1 August 2017 | 4 May 2018 |
| Phase 2 | NCT02679456 | Safety and Efficacy of Oral Ibrexafungerp (SCY-078) vs. Oral Fluconazole in Subjects With Vulvovaginal Candidiasis | | 96 | SCY-078 & Fluconazole | Percentage of subjects achieving therapeutic cure at TOC visit (Day 24 +/-3)% of subjects with recurrence of VVC during the observation period | 1 November 2015 | 5 August 2016 |
| Phase 3 | NCT03734991 | Efficacy and Safety of Oral Ibrexafungerp (SCY-078) vs. Placebo in Subjects With Acute Vulvovaginal Candidiasis (VANISH 303) | Vanish 303 | 376 | Ibrexafungerp and Placebo | Clinical cure (complete resolution of signs and symptoms) Mycological eradication (negative culture for yeast growth) Clinical cure and mycological eradication (responder outcome) Complete resolution of signs and symptoms at follow-up subjects with treatment-related adverse events | 4 January 2019 | 4 September 2019 |
| Phase 3 | NCT03987620 | Efficacy and Safety of Oral Ibrexafungerp (SCY-078) vs. Placebo in Subjects With Acute Vulvovaginal Candidiasis | Vanish 306 | 366 | Ibrexafungerp and Placebo | Clinical cure (complete resolution of signs and symptoms) Mycological eradication (negative culture for growth of yeast) Clinical cure and mycological eradication (responder outcome) Complete resolution of signs 7 symptoms at follow-up Safety and tolerability of Ibrexafungerp | 7 June 2019 | 29 April 2020 |
| Phase 3 | NCT04029116 | Phase 3 Study of Oral Ibrexafungerp (SCY-078) vs. Placebo in Subjects With Recurrent Vulvovaginal Candidiasis (VVC) | CANDLE | 320 | | Clinical Success The percentage of subjects with no Mycologically Proven Recurrence Safety and tolerability | 23 September 2019 | September 2021 |

Ibrexafungerp tablets were approved by the FDA in June 2021 for oral use in patients with vulvovaginal candidiasis (VVC), also known as a vaginal yeast infection. The recommended dosage is 600 mg, divided into two 150 mg pills twice a day for one day. Oral Ibrexafungerp indicated efficacy and a favorable tolerability profile in women with VVC in two Phase 3 studies, according to the FDA. The FDA granted approval based on the results of the VANISH-303 and VANISH-306 multicenter randomized, double-blind, placebo-controlled investigations, in which oral Ibrexafungerp indicated efficacy and an acceptable tolerability profile in women with VVC.

The Phase 3 research VANISH-303 (clinicaltrials.gov: NCT03734991) enrolled 376 women in the United States. The preliminary findings have been shared. Ibrexafungerp 300 mg was compared to a placebo BID in this one-day research. Ibrexafungerp considerably outperformed placebo in terms of clinical cure (full remission of all vaginal signs and symptoms by Day 10) and mycological eradication test-of-cure (TOC). On Day 10, the efficacy was comparable to the Phase 2 DOVE study. Ibrexafungerp was found to be generally safe and well-tolerated, with the most prevalent side effects being gastrointestinal. Severe and major AEs were uncommon with Ibrexafungerp and more common with placebo. VANISH-306 (NCT03987620) was a Phase 3 research that enrolled 376 women in the United States and the European Union. Ibrexafungerp 300 mg BID or placebo were given to the women for one day. Ibrexafungerp considerably outperformed placebo in terms of clinical cure (full remission of all vaginal signs and symptoms by Day 10) and mycological eradication test-of-cure (TOC). Ibrexafungerp was generally well-tolerated and safe, with no major adverse effects reported. CANDLE (clinicaltrials.gov: NCT04029116) is a 320-woman Phase 3 randomized, double-blind study. Oral Ibrexafungerp 300 mg or placebo twice daily for 1 day each month for 6 months are the study arms.

The high cost of novel antifungals restricts their availability, particularly in low- and middle-income countries (LMICs), where the fungal disease burden is large, but the perceived commercial market is modest, limiting manufacturers' interest in obtaining more regulatory approvals⁶⁵. Ibrexafungerp has been tested in healthy individuals in many Phase 1 studies. Once-daily dose, a reduced likelihood of drug-drug interactions, high tissue concentrations, and a favorable safety/tolerability profile are all supported by the PK profile. The clinical development program for VVC showed significant clinical cure rates and a low rate of primarily GI AEs when employing a twice-daily dose regimen to minimize GI intolerance. Ibrexafungerp is the first of a new class of triterpenoid antifungals with a novel mechanism of action (MOA), glucan synthase inhibition, that distinguishes it from current azole therapies for VVC. *In vitro*, Ibrexafungerp showed fungicidal activity against *Candida spp.*, including azole-resistant isolates, that was comparable to echinocandins.

CONCLUSIONS

Finally, unlike other drugs that show greater MICs in low pH conditions *in vitro*, Ibrexafungerp has shown good action at low pH *in vitro* testing environments, equivalent to the low vaginal pH in VVC. Ibrexafungerp has a favorable tolerability profile, with the majority of recorded adverse events (AEs) being gastrointestinal and often minor, and not leading to treatment cessation. Another area where a novel class of fungicidal agents could be advantageous is recurrent VVC, which has a significant impact on QoL. Ibrexafungerp provides a novel mechanism of action with a broader antifungal spectrum, fungicidal activity against *Candida spp.*, high tissue penetration into target tissues, activity at low pH, and no preclinical fetal toxicity, which addresses many of the unmet needs of existing antifungal drugs for VVC. Ibrexafungerp patent applications are in the works for 10 years of regulatory exclusivity in the United States, as well as a composition-of-matter patent that will last until 2035, with more applications pending for a total of 15 years of exclusivity in the United States⁶⁶. This will further delay access to this therapy in most LMIC nations; thus, to promote worldwide access to this breakthrough medication, early and effective partnerships among pharmaceutical companies, governments, and international organizations are required. Despite this, the current approval of Ibrexafungerp relies on the fact that this novel antifungal provides the VVC treating clinician and their patients with the first non-azole, one-day treatment option for women with VVC who do not respond to azoles or who are allergic or intolerant to azole therapy.

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Not applicable.

AVAILABILITY OF DATA AND MATERIAL:

Not applicable.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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REFERENCES

- Barajas JF, Wehrs M, To M, Cruickshanks L, Urban R, McKee A, Gladden J, Goh EB, Brown ME, Pierotti D, Carothers JM, Mukhopadhyay A, Keasling JD, Fortman JL, Singer SW, Bailey CB. Isolation and Characterization of Bacterial Cellulase Producers for Biomass Deconstruction: A Microbiology Laboratory Course. *J Microbiol Biol Educ* 2019;20:20.2.34.
- Sobel JD. Vulvovaginal candidiasis. *Lancet* 2007; 369: 1961-1971.
- Gonçalves B, Ferreira C, Alves CT, Henriques M, Azeredo J, Silva S. Vulvovaginal candidiasis: Epidemiology, microbiology and risk factors. *Crit Rev Microbiol* 2016; 42: 905-927.
- Felix TC, de Brito Röder DVD, Dos Santos Pedrosa R. Alternative and complementary therapies for vulvovaginal candidiasis. *Folia Microbiol (Praha)* 2019; 64: 133-141.
- Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Candida vaginitis: self-reported incidence and associated costs. *Sex Transm Dis* 2000; 27: 230-235.
- Achkar JM, Fries BC. Candida infections of the genitourinary tract. *Clin Microbiol Rev* 2010; 23: 253-273.
- Anderson MR, Klink K, Cochrane A. Evaluation of vaginal complaints. *JAMA* 2004; 291: 1368-1379.
- Fidel PL Jr, Sobel JD. Immunopathogenesis of recurrent vulvovaginal candidiasis. *Clin Microbiol Rev* 1996; 9: 335-348.
- Hurley R, de Louvois J. Candida vaginitis. *Postgrad Med J* 1979; 55: 645-647.
- Foxman B, Marsh JV, Gillespie B, Sobel JD. Frequency and response to vaginal symptoms among white and African American women: results of a random digit dialing survey. *J Womens Health* 1998; 7: 1167-1174.
- Blostein F, Levin-Sparenberg E, Wagner J, Foxman B. Recurrent vulvovaginal candidiasis. *Ann Epidemiol* 2017; 27: 575-582.e3.
- Witkin SS. Immunologic factors influencing susceptibility to recurrent candidal vaginitis. *Clin ObstetGynecol* 1991; 34: 662-668.
- Sobel JD, Faro S, Force RW, Foxman B, Ledger WJ, Nyirjesy PR, Reed BD, Summers PR. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. *Am J Obstet Gynecol* 1998; 178: 203-211.
- Nyirjesy P, Zhao Y, Ways K, Usiskin K. Evaluation of vulvovaginal symptoms and Candida colonization in women with type 2 diabetes mellitus treated with canagliflozin, a sodium glucose cotransporter 2 inhibitor. *Curr Med Res Opin* 2012; 28: 1173-1178.
- Sobel J. Current treatment options for vulvovaginal candidiasis. *Womens Health (Lond)* 2005; 1: 253-261.
- Pappas PG, Kauffman CA, Andes DR. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. *Clin Infect Dis* 2016; 62: e1-50.
- Marchaim D, Lemanek L, Bheemreddy S, Kaye KS, Sobel JD. Fluconazole-resistant *Candida albicans* vulvovaginitis. *ObstetGynecol* 2012; 120: 1407-1414.
- Bérard A, Sheehy O, Zhao JP, Gorgui J, Bernatsky S, de Moura CS, Abrahamowicz M. Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. *CMAJ* 2019; 191: E179-E187.
- Sobel JD, Sobel R. Current treatment options for vulvovaginal candidiasis caused by azole-resistant *Candida* species. *Expert Opin Pharmacother* 2018; 19: 971-977.
- Wu Y, Li C, Wang Z. Clonal spread and azole-resistant mechanisms of non-susceptible *Candida albicans* isolates from vulvovaginal candidiasis patients in three Shanghai maternity hospitals. *Med Mycol* 2018; 56: 687-694.
- Yao D, Chen J, Chen W. Mechanisms of azole resistance in clinical isolates of *Candida glabrata* from two hospitals in China. *Infect Drug Resist* 2019; 12: 771-781.
- Pfaller MA, Messer SA, Motyl MR, Jones RN, Castanheira M. 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* 2013; 57: 1065-1068.
- Jiménez-Ortigosa C, Perez WB, Angulo D. 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* 2017; 61: e00833-17.
- Berkow EL, Angulo D, Lockhart SR. In Vitro Activity of a Novel Glucan Synthase Inhibitor, SCY-078, against Clinical Isolates of *Candida auris*. *Antimicrob Agents Chemother* 2017; 61: e00435-17.
- Ghannoum M, Long L, Isham N, Hager C, Wilson R, Borroto-Esoda K, Barat S, Angulo D. Activity of a novel 1,3-beta-D-glucan Synthase Inhibitor, Ibrexafungerp (formerly SCY-078), Against *Candida glabrata*. *Antimicrob Agents Chemother* 2019; 63: e01510-19.
- Ghannoum M, Long L, Larkin EL. Evaluation of the antifungal activity of the novel oral glucan synthase inhibitor SCY-078, singly and in combination, for the treatment of invasive *Aspergillus* infection. *Antimicrob Agents Chemother* 2018; 62: e00244-18.
- Larkin E, Hager C, Chandra J. 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* 2017; 61: e02396-16.
- Marcos-Zambrano LJ, Gómez-Perosanz M, Escribano P. The novel oral glucan synthase inhibitor SCY-078 shows in vitro activity against sessile and planktonic *Candida* spp. *J Antimicrob Chemother* 2017; 72: 1969-1976.
- Nunnally NS, Etienne KA, Angulo D. In vitro activity of ibrexafungerp, a novel glucan synthase inhibitor against *Candida glabrata* isolates with FKS mutations. *Antimicrob Agents Chemother* 2019; 63: e01692-19.
- Pfaller MA, Messer SA, Rhomberg PR. Differential activity of the oral glucan synthase inhibitor SCY-078 against wild-type and echinocandin-resistant strains of *Candida* species. *Antimicrob Agents Chemother* 2017; 61: e00161-17.
- Rautermaa-Richardson R, Moore CB, Rawson K. *Aspergillus* isolates from patients with chronic pulmonary aspergillosis mycologically and clinically resistant to azole antifungals are sensitive to Ibrexafungerp(SCY-078). Poster presented at the 9th Congress on Trends in Medical Mycology, October 11-14, 2019, Nice, France.
- Scorneaux B, Angulo D, Borroto-Esoda K. SCY-078 is fungicidal against *Candida* species in time-kill studies. *Antimicrob Agents Chemother* 2017; 61: e01961-16.
- Wiederhold NP, Najvar LK, Jaramillo R. 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* 2018; 73: 448-451.
- Peláez F, Cabello A, Platas G, Díez MT, González del Val A, Basilio A, Martán I, Vicente F, Bills GE, Giacobbe RA, Schwartz RE, Onish JC, Mainz MS, Abruzzo GK, Flattery AM, Kong L, Kurtz MB. The discovery of enfumafungin, a novel antifungal compound produced by an endophytic *Horomonema* species biological activity and taxonomy of the producing organisms. *Syst Appl Microbiol* 2000; 23: 333-343.
- PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary. Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/> (accessed on 30 December 2020).
- Coad BR, Lamont-Friedrich SJ, Gwynne L, Jasieniak M, Griesser SS, Traven A, Peleg AY, Griesser HJ. Surface coatings with covalently attached caspofungin are effective in eliminating fungal pathogens. *J Mater Chem B* 2015; 3: 8469-8476.

37. Onishi J, Meinz M, Thompson J, Curotto J, Dreikorn S, Rosenbach M, Douglas C, Abruzzo G, Flattery A, Kong L, Cabello A, Vicente F, Pelaez F, Diez MT, Martin I, Bills G, Giacobbe R, Dombrowski A, Schwartz R, Morris S, Harris G, Tsiouras A, Wilson K, Kurtz MB. Discovery of novel antifungal (1,3)-beta-D-glucan synthase inhibitors. *Antimicrob Agents Chemother* 2000; 44: 368-377.
38. Davis MR, Donnelley MA, Thompson GR. Ibrexafungerp: A novel oral glucan synthase inhibitor. *Med Mycol* 2020; 58: 579-592.
39. Azie N. A Phase 2b, Dose Finding Study Evaluating Oral Ibrexafungerp in Moderate to Severe Acute Vulvovaginal Candidiasis (DOVE). In Proceedings of the 3rd ISIDOG Congress, Porto, Portugal, 31 October–3 November 2019. Available online: <https://www.scynexis.com/science/publications-and-presentations/posters-and-presentations?page=2> (accessed on 29 December 2020).
40. Apgar JM, Wilkening RR, Parker DL Jr, Meng D, Wildonger KJ, Sperbeck D, Greenlee ML, Balkovec JM, Flattery AM, Abruzzo GK, Galdoci AM, Giacobbe RA, Gill CJ, Hsu MJ, Liberator P, Misura AS, 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. Ibrexafungerp: An orally active β -1,3-glucan synthesis inhibitor. *Bioorg Med Chem Lett* 2021; 32: 127661.
41. Pfaller MA, Messer SA, Motyl MR, Jones RN, Castanheira M. 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* 2013; 57: 1065-1068.
42. Walker SS, Xu Y, Triantafyllou I, Waldman MF, Mendrick C, Brown N, Mann P, Chau A, Patel R, Bauman N, Norris C, Antonacci B, Gurnani M, Cacciapuoli A, McNicholas PM, Wainhaus S, Herr RJ, Kuang R, Aslanian RG, Ting PC, Black TA. Discovery of a novel class of orally active antifungal beta-1,3-D-glucan synthase inhibitors. *Antimicrob Agents Chemother* 2011; 55: 5099-106.
43. Davis MR, Donnelley MA, Thompson GR. Ibrexafungerp: A novel oral glucan synthase inhibitor. *Med Mycol* 2020; 58: 579-592.
44. Wring S, Murphy G, Atiee G. Clinical pharmacokinetics and drug-drug interaction potential for coadministered SCY-078, an oral fungicidal glucan synthase inhibitor, and tacrolimus. *Clin Pharmacol Drug Dev* 2019; 8: 60-69.
45. Wring S, Murphy G, Atiee G. 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* 2018; 58: 1305-1313.
46. Murphy G, Hyman M, Willett M. CYP-mediated drug interaction profile of SCY-078, a novel glucan synthase inhibitor (GSI).
47. Murphy G, Darpo B, Marbury T. Lack of an effect of SCY-078 a novel antifungal agent on QTc interval in healthy subjects.
48. Trucksis M, Garrett G, Bautmans A. A phase I multiple rising dose study evaluating safety, tolerability, and pharmacokinetics of MK-3118, oral glucan synthase inhibitor, in healthy volunteers. 51st Inter science Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2011; Chicago, Illinois, USA. Poster no. F1-1390.
49. Danby CS, Boikov D, Rautemaa-Richardson R, Sobel JD. Effect of pH on in vitro susceptibility of *Candida glabrata* and *Candida albicans* to 11 antifungal agents and implications for clinical use. *Antimicrob Agents Chemother* 2012; 56: 1403-1406.
50. Rodríguez-Cerdeira C, Gregorio MC, Molares-Vila A, López-Barcenas A, Fabbrocini G, Bardhi B, Sinani A, Sánchez-Blanco E, Arenas-Guzmán R, Hernandez-Castro R. Biofilms and vulvovaginal candidiasis. *Colloids Surf B Biointerfaces* 2019; 174: 110-125.
51. Makanjuola O, Bongomin F, Fayemiwo SA. An Update on the Roles of Non-albicans *Candida* Species in Vulvovaginitis. *J Fungi (Basel)* 2018; 4: 121.
52. Barat S, Borroto-Esoda AD, Angulo D. Ibrexafungerp (SCY-078): a first-in-class, orally-bioavailable, glucan synthase inhibitor has fungicidal activity against *C. auris*, an emerging multidrug-resistant pathogen. Poster presented at the 2018 Mycoses Study Group Education and Research Consortium, Big Sky, Montana.
53. Scorneaux B, Angulo D, Borroto-Esoda K, Ghannoum M, Peel M, Wring S. SCY-078 Is Fungicidal against *Candida* Species in Time-Kill Studies. *Antimicrob Agents Chemother* 2017; 61: e01961-16.
54. Schell WA, Jones AM, Borroto-Esoda K, Alexander BD. Antifungal Activity of SCY-078 and Standard Antifungal Agents against 178 Clinical Isolates of Resistant and Susceptible *Candida* Species. *Antimicrob Agents Chemother* 2017; 61: e01102-17.
55. Jiménez-Ortigosa C, Moore C, Denning DW, Perlin DS. Emergence of Echinocandin Resistance Due to a Point Mutation in the *fks1* Gene of *Aspergillus fumigatus* in a Patient with Chronic Pulmonary Aspergillosis. *Antimicrob Agents Chemother* 2017; 61: e01277-17.
56. Jiménez-Ortigosa C, Perez WB, Angulo D, Borroto-Esoda K, Perlin DS. 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* 2017; 61: e00833-17.
57. Perlin DS. Resistance to echinocandin-class antifungal drugs. *Drug Resist Updat* 2007; 10: 121-130.
58. Roman M, Hernandez C, Blanco D. SCY-078 phase 2 study in moderate and severe vulvovaginal candidiasis. 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 2017; Vienna, Austria. Poster P1748, Big Sky, Montana.
59. Njirjesy P, Cadel R, Tufa M. A phase 2b, dose-finding study evaluating oral ibrexafungerp in vulvovaginal candidiasis. Poster presented at the American College of Obstetrics and Gynecology Annual Clinical and Scientific Meeting, May 3-6, 2019, Nashville, TN.
60. Schell WA, Jones AM, Borroto-Esoda K, Alexander BD. Antifungal Activity of SCY-078 and Standard Antifungal Agents against 178 Clinical Isolates of Resistant and Susceptible *Candida* Species. *Antimicrob Agents Chemother* 2017; 61: e01102-17.
61. Cadet R, Tufa M, Angulo D, Nyirjesy P. A Phase 2b, Dose-Finding Study Evaluating Oral Ibrexafungerp vs Fluconazole in Vulvovaginal Candidiasis (DOVE). *Obstet Gynecol* 2019; 133: 113S-114S.
62. Schwebke JR, Sorkin-Wells V, Azie N, Angulo D, Sobel J. Oral ibrexafungerp efficacy and safety in the treatment of vulvovaginal candidiasis: A phase 3, randomized, blinded, study vs. placebo (VANISH-303). *IDSOG Oral Present* 2020; 223: 964-965.
63. Scynexis. SCYNEXIS Announces Positive Top-Line Results from Its Second Pivotal Phase 3 Study (VANISH-306) of Oral Ibrexafungerp for the Treatment of Vulvovaginal Candidiasis (Vaginal Yeast Infection). SCYNEXIS, Inc. Press Release Online. 2020.
64. Scynexis. SCYNEXIS Announces FDA Acceptance and Priority Review of New Drug Application for Oral Ibrexafungerp for the Treatment of Vaginal Yeast Infections. SCYNEXIS, Inc. Press Release Online. 2020.
65. Kneale M, Bartholomew JS, Davies E, Denning DW. Global access to antifungal therapy and its variable cost. *J Antimicrob Chemother* 2016; 71: 3599-3606.
66. Scynexis. Ibrexafungerp: First Representative of a Novel Oral/IV Antifungal Family (vF_SCYX Corporate Presentation-Dec.2020.pdf). Corporate Presentation—Dec. 2020 Online. 2020.