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CLINICAL THERAPEUTICS

# A Novel 1,3-Beta-D-Glucan Inhibitor, Ibrexafungerp (Formerly SCY-078), Shows Potent Activity in the Lower pH Environment of Vulvovaginitis

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**ABSTRACT** Ibrexafungerp (IBX) (formerly SCY-078) is a novel glucan synthase inhibitor whose oral availability is being evaluated for efficacy against vulvovaginal candidiasis (VVC). Bioavailability and *in vitro* activity are important efficacy indicators, but accepted susceptibility methods do not always accurately predict activity in an acidic environment, such as the vagina. Studies were 3-fold, as follows: (i) pharmacokinetic study following oral administration in a murine model; (ii) susceptibility testing of isolates from a phase 2 VVC clinical trial by CLSI M27-A4 methodology; and (iii) susceptibility testing of *Candida albicans* and *Candida glabrata* isolates obtained from this trial group in RPMI 1640 adjusted to 3 different pH values, 7.0, 5.72, and 4.5, compared to susceptibility testing for micafungin and fluconazole. IBX readily accumulated in vaginal tissues and secretions following oral administration. Potent *in vitro* activity was demonstrated against *Candida* strains obtained at baseline and end of study visits. Moreover, the geometric mean (GM) values for IBX at pH 4.5 were dramatically lower than those at pH 7.0 and 5.72. The $MIC_{90}$ values of micafungin remained the same regardless of pH value, while those of fluconazole tended to increase with lower pH values. IBX is able to reach target tissues following oral administration at pharmacologically meaningful levels. IBX demonstrated potent *in vitro* activity, with no development of resistance, following repeated exposure over the course of the clinical trial. Importantly, activity of IBX in an acidic medium suggests a therapeutic advantage of this novel antifungal in the treatment of vaginal *Candida* infections.

**KEYWORDS** ibrexafungerp, SCY-078, vulvovaginitis

Vulvovaginal candidiasis (VVC) accounts for up to one-third of all vaginitis reported in the United States (1, 2) and is recurrent in 5% to 9% of patients (3). Although most cases of VVC are caused by *Candida albicans*, *Candida glabrata* and less commonly fluconazole (FLU)-resistant *C. albicans* are also causes of recurrent cases (4). *C. glabrata* has shown intrinsic resistance to multiple azoles, including FLU, which is widely used for treatment of this infection. Thus, eradication of FLU-resistant *C. albicans* and *C. glabrata* from the vagina has proven difficult (4).

Complicating the task of choosing appropriate therapy is the fact that the accepted antifungal broth dilution susceptibility method, Clinical and Laboratory Standards Institute (CLSI) M27-A4 (5), does not always predict resistance in test isolates from cases of VVC. It is thought that this disconnect may be due to the unique acidic vaginal environment, which may influence antifungal activity. CLSI broth dilution susceptibility testing is conducted in a medium buffered to a pH of 7.0, while the normal pH of the vagina, 4 to 4.5, remains acidic during VVC episodes (6). To that point, Marr et al. have

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**TABLE 1** Ibrexafungerp plasma: tissue concentration ratio and accumulation potential[a]

| Dose group | p.o. regimen (mg/kg single dose) | Total doses (no.) | $AUC_{0-24}$ (μg · h/ml) mean ± SD for: | | |
|---|---|---|---|---|---|
| | | | Plasma | Vaginal secretions | Vaginal tissue |
| 1 | 10 | 1 | 8.4 ± 1.5 | 1.3 ± 0.7 | 29.4 ± 18.1 |
| 2 | 20 | 1 | 19.4 ± 3.3 | 1.8 ± 1.4 | 54.1 ± 14.1 |
| 3 | 40 | 1 | 36.1 ± 7.0 | 4.2 ± 2.8 | 186.8 ± 107.7 |
| 4 | 80 | 1 | 75.6 ± 12.4 | 10.8 ± 8.4 | 168.9 ± 36.3 |

[a]p.o., oral; $AUC_{0-24}$, area under the concentration-time curve from 0 to 24 h.

shown that an acidic pH tends to result in higher MICs of FLU for some *Candida* species (7), which in turn may indicate true FLU resistance.

Ibrexafungerp (IBX) (formerly SCY-078) is a member of a new class of glucan synthase inhibitors that interferes with the synthesis of the fungal cell wall polymer β-(1,3)-D-glucan. IBX is currently in clinical development for use in the treatment of various fungal infections and is available as oral and intravenous formulations. *In vitro* studies have demonstrated that IBX has fungicidal activity against azole-resistant *Candida* spp. isolates similar to the echinocandins but, importantly, shows activity against the majority of clinical isolates demonstrating echinocandin resistance due to *FKS* gene mutations (8).

IBX has also shown broad-spectrum activity against *Aspergillus* strains (9), and while these *in vitro* tests would predict therapeutic success in cases such as invasive candidiasis or aspergillosis, the effect of an acidic environment on the activity of IBX is not known.

In order to further characterize the activity of IBX in the treatment of vulvovaginitis, we evaluated the potential for vaginal distribution of orally administered IBX in mice, while simultaneously determining whether changes in test medium pH that mimic the vaginal environment had an effect on the *in vitro* susceptibility of *C. albicans* and *C. glabrata* vaginal isolates as measured by MIC. Additionally, we evaluated the MICs of *Candida* spp. isolates from patients with VVC before and after IBX therapy to make an initial assessment of the risk of resistance development.

## RESULTS

**Pharmacokinetic studies.** IBX demonstrated a high potential to accumulate in vaginal tissues and fluids following oral administration, with concentrations in both increasing in a dose-dependent manner. The content of IBX in vaginal tissue was 2- to 5-fold higher than the respective plasma levels across all dose groups (Table 1).

***In vitro* activity of IBX at various pH levels.** MIC ranges for IBX at pH values of 7.0, 5.72, and 4.5 against the *C. albicans* isolates were 0.125 to 0.5 μg/ml, 0.125 to 0.25 μg/ml, and <0.016 to 0.031 μg/ml, respectively. The $MIC_{50}$ values (defined as the lowest concentration to inhibit 50% of isolates tested) for IBX at pH values 7.0 and 5.72 were both 0.25 μg/ml, while the $MIC_{90}$ values (defined as the lowest concentration to inhibit 90% of isolates tested) were 0.5 and 0.25 μg/ml at pH 7.0 and 5.72, respectively. The $MIC_{50}$ and $MIC_{90}$ values for IBX at pH 4.5 were both <0.016 μg/ml. The geometric mean (GM) of the MIC values for IBX against the *C. albicans* isolates tested at pH 4.5 was significantly lower than those at pH 7.0 and 5.72 (*P* values of <0.0001) (Table 2).

**TABLE 2** MIC results for IBX, MICA, and FLU against 10 *C. albicans* isolates tested at three pH levels

| Parameter | Results (μg/ml) for IBX with pH: | | | Results (μg/ml) for MICA[a] with pH: | | | Results (μg/ml) for FLU[b] with pH: | | |
|---|---|---|---|---|---|---|---|---|---|
| | 7.0 | 5.72 | 4.5 | 7.0 | 5.72 | 4.5 | 7.0 | 5.72 | 4.5 |
| Range | 0.125–0.5 | 0.125–0.25 | <0.016–0.031 | 0.25 | 0.063–1 | 0.25–0.5 | <0.125–1 | <0.125–1 | 0.25–8 |
| $MIC_{50}$ | 0.25 | 0.25 | <0.016 | 0.25 | 1 | 0.5 | 0.25 | <0.125 | 0.25 |
| $MIC_{90}$ | 0.5 | 0.25 | <0.016 | 0.25 | 1 | 0.5 | 0.25 | 0.25 | 1 |
| GM | 0.250 | 0.218 | 0.017 | 0.250 | 0.575 | 0.467 | 0.315 | 0.397 | 0.500 |

[a]MICA, micafungin.
[b]FLU, fluconazole.

**TABLE 3** MIC results for IBX, MICA, and FLU against 10 *C. glabrata* isolates tested at three pH levels

| Parameter | Results ($\mu$g/ml) for IBX with pH: | | | Results ($\mu$g/ml) for MICA[a] with pH: | | | Results ($\mu$g/ml) for FLU[b] with pH: | | |
|---|---|---|---|---|---|---|---|---|---|
| | 7.0 | 5.72 | 4.5 | 7.0 | 5.72 | 4.5 | 7.0 | 5.72 | 4.5 |
| Range | 0.5–1 | 0.5 | 0.031–0.063 | 0.25–0.5 | 0.25 | 0.25 | 0.5–2 | 2–16 | 1–16 |
| $MIC_{50}$ | 1 | 0.5 | 0.063 | 0.25 | 0.25 | 0.25 | 1 | 8 | 8 |
| $MIC_{90}$ | 1 | 0.5 | 0.063 | 0.5 | 0.25 | 0.25 | 2 | 16 | 16 |
| GM | 0.758 | 0.500 | 0.051 | 0.308 | 0.250 | 0.250 | 1.231 | 6.964 | 8.000 |

[a]MICA, micafungin.
[b]FLU, fluconazole.

MIC ranges for IBX at pH values of 7.0, 5.72, and 4.5 against the *C. glabrata* isolates were 0.5 to 1.0 $\mu$g/ml, 0.5 $\mu$g/ml, and 0.031 to 0.063 $\mu$g/ml, respectively. The $MIC_{50}$ and $MIC_{90}$ values for IBX at pH 7.0 were both 1.0 $\mu$g/ml, while the $MIC_{50}$ and $MIC_{90}$ values for IBX at pH 5.72 were one dilution lower (0.5 $\mu$g/ml). The $MIC_{50}$ and $MIC_{90}$ values for IBX at pH 4.5 were both 0.063 $\mu$g/ml. In this model system, the GM of the MIC values for IBX against the *C. glabrata* isolates tested at pH 4.5 was also significantly lower than those at pH 7.0 and 5.72 (*P* values of $<0.0001$) (Table 3).

MIC ranges for micafungin (MICA) at pH values of 7.0, 5.72, and 4.5 against the *C. albicans* isolates were 0.25 $\mu$g/ml, 0.063 to 1.0 $\mu$g/ml, and 0.25 to 0.5 $\mu$g/ml, respectively. The $MIC_{50}$ and $MIC_{90}$ values of MICA against *C. albicans* were equal at each pH level (pH 7.0, $MIC_{50}$ and $MIC_{90}$ = 0.25 $\mu$g/ml; pH 5.72, $MIC_{50}$ and $MIC_{90}$ = 1.0 $\mu$g/ml; pH 4.5, $MIC_{50}$ and $MIC_{90}$ = 0.5 $\mu$g/ml) (Table 3). The MIC range for MICA against *C. glabrata* isolates was 0.25 to 0.5 $\mu$g/ml at pH 7.0, while all MIC values were 0.25 $\mu$g/ml at pH 5.72 and 4.5. The $MIC_{90}$ of MICA at pH 7.0 was one dilution higher at 0.5 $\mu$g/ml (Table 3).

MIC ranges for FLU against the *C. albicans* isolates were $<0.125$ to 1.0 $\mu$g/ml at pH values of 7.0 and 5.72 and 0.25 to 8.0 $\mu$g/ml at pH 4.5. The FLU $MIC_{50}$ and $MIC_{90}$ values were 0.25 $\mu$g/ml at pH 7.0; $<0.125$ and 0.25 $\mu$g/ml, respectively, at pH 5.72; and 0.25 and 1.0 $\mu$g/ml, respectively, at pH 4.5 (Table 3). MIC ranges for FLU at pH values of 7.0, 5.72, and 4.5 against the *C. glabrata* isolates were 0.5 to 2.0 $\mu$g/ml, 2.0 to 16 $\mu$g/ml, and 1.0 to 16 $\mu$g/ml, respectively. The $MIC_{50}$ values of FLU were 1.0 $\mu$g/ml at pH 7.0 and 8 $\mu$g/ml at pH 5.72 and pH 4.5, while the $MIC_{90}$ values were each one dilution higher (2 $\mu$g/ml at pH 7.0 and 16 $\mu$g/ml at pH 5.72 and pH 4.5) (Table 3).

**Activity of IBX against baseline versus end of therapy collected clinical trial isolates.** MICs of IBX were determined against all isolates obtained from a phase 2 dose-finding clinical trial involving subjects with acute vulvovaginal candidiasis (ClinicalTrials.gov identifier NCT02679456). The majority of subjects in the study had *C. albicans* detected at baseline (86%). Other *Candida* species isolated at baseline included *Candida parapsilosis*, *C. glabrata*, *Candida krusei*, *Candida tropicalis*, *Candida lusitaniae*, and *Candida nivariensis*. The study included 50 subjects with recurrent VVC (RVVC) that received oral IBX and for which vaginal cultures were positive for *Candida* spp. at baseline with subsequent cultures scheduled 1, 2, 3, and 4 months after treatment. These study results have been previously reported showing high clinical cure rates (i.e., 76%) with the oral IBX regimens tested (S. Helou and D. Angulo, A multicenter randomized, evaluator blinded, active-controlled study to evaluate the safety and efficacy of oral SCY-078 vs. oral fluconazole in 96 subjects with moderate to severe vulvovaginal candidiasis, presented at the Infectious Diseases Society for Obstetrics and Gynecology 44th Annual Meeting, Park City, UT, August 2017).

The IBX MIC range, $MIC_{50}$, and $MIC_{90}$ for baseline *C. albicans* isolates among the IBX-treated groups (43/50; 86%) were 0.06 to 0.5 $\mu$g/ml, 0.25 $\mu$g/ml, and 0.25 $\mu$g/ml, respectively. Thirty-one of the 43 IBX-treated subjects (72%) with *C. albicans* infection experienced mycological eradication. Overall, there were no changes in MIC values obtained for the *C. albicans* isolates from the 12 subjects with positive culture at the end of the study; the IBX MIC range, $MIC_{50}$, and $MIC_{90}$ were 0.06 to 0.5 $\mu$g/ml, 0.25 $\mu$g/ml, and 0.25 $\mu$g/ml, respectively (Table 4).

**TABLE 4** Distribution of IBX MICs against *C. albicans* isolates collected at baseline and from per protocol patients on study drug at the last visit

| | No. of isolates with IBX MIC: | | | |
|---|---|---|---|---|
| **Time of collection** | **0.06 μg/ml** | **0.125 μg/ml** | **0.25 μg/ml** | **0.5 μg/ml** |
| Baseline ($n = 43$) | 1 | 16 | 25 | 1 |
| Last visit ($n = 9$) | | 2 | 7 | |

## DISCUSSION

VVC and recurrent VVC (RVVC) are serious conditions with significant morbidity and with very limited oral treatment options. VVC affects approximately 70% to 75% of women at least once in their lifetime (3), and RVVC, defined as 3 or more episodes of symptomatic acute *Candida* vaginitis in a 12-month period, is estimated to occur in 6% to 9% of women during their reproductive years (10). There is no product approved for the prevention of RVVC, and current treatment alternatives have significant limitations for the treatment of VVC, particularly in patients with other comorbidities, in patients taking prohibited concomitant medications, during pregnancy, or for episodes caused by an azole-resistant microorganism.

Single dosing of FLU has long been shown to produce efficacious concentrations in vaginal secretions (11, 12), with a reported clinical cure rate of 69%. However, according to the Centers for Disease Control and Prevention, conventional antifungal treatment may not be effective against *C. glabrata* and other non-*albicans Candida* species observed in 10% to 20% of women with recurrent VVC (13). Further, antifungals normally prescribed for treatment do not always eradicate the total *Candida* population, likely due to their fungistatic properties, leaving a reservoir for the establishment of a recurring infection (14).

*In vitro* susceptibility data showing decreased activity of certain antifungals at lower pH levels may explain the high rates of *Candida* survival in the acidic vaginal environment. Establishing an alternative susceptibility standard employing a lower pH medium to accurately predict therapeutic outcome would be lengthy and cost prohibitive to develop and standardize; thus, identifying a novel compound that is efficacious against *Candida* at lower pH would be highly advantageous. In this study, we compared the MICs of IBX, a novel glucan synthase inhibitor, to those of FLU against *C. albicans* and *C. glabrata* strains isolated from patients with recurrent vulvovaginitis. Though not a therapeutic agent for vaginitis due to its intravenous application, we also took the opportunity to include an echinocandin, MICA, as a comparator in order to provide additional data for this drug at different pH levels.

Interestingly, IBX showed significantly increased activity against the *C. albicans* and *C. glabrata* strains in an acidic medium. IBX MIC values at pH 4.5 were up to 5-fold lower than those at pH values of 7.0 and 5.72 for both *C. glabrata* and *C. albicans* strains. The opposite effect was seen with FLU, for which the MICs tended to be higher at the lower pH levels. These data agree with those of Danby et al., who reported elevated MIC values at pH 4.5 for FLU, voriconazole (VOR), and posaconazole (15). Similar data have been published for clotrimazole and miconazole as well as FLU (16). Combined, these data indicate that FLU is less effective at eradicating these yeast strains in acidic environments, such as the vagina, and suggest a therapeutic advantage of IBX in the treatment of vaginal *Candida* infections.

Further, our data show that pH levels had no effect on the activity of MICA. The $MIC_{50}$ and $MIC_{90}$ values of MICA against both *Candida* species were within 2 dilutions at all pH levels (a 2-dilution variance is considered equivalent). These results suggest that IBX may inhibit glucan synthase in an alternative manner to that of echinocandins, perhaps due to its different molecular structure. In addition to possessing antifungal activity at a wide pH range, IBX has an advantage over MICA and other echinocandins because of its bioavailability in an oral formulation.

Importantly, the levels of IBX accumulation, even at the lowest testing dose of 10 mg of drug/kg of body weight in the murine model, were more than 2.5 times greater in

vaginal secretions than at the highest MIC value obtained from clinical trial isolates and 53 times greater in vaginal tissue. These data, coupled with the lack of resistance development following repeated exposure and a previously reported capacity to reduce kidney fungal burden in a murine model (17), suggest that IBX has utility for treatment of VVC.

## MATERIALS AND METHODS

**Pharmacokinetic studies.** A dispositional pharmacokinetics study with IBX was conducted in female CD-1 mice following oral (gavage) dosing. Mice ($n = 27$ per group) were dosed with a single dose of IBX at 10, 20, 40, or 80 mg/kg. Whole blood, vaginal lavage fluid, and vulvovaginal tissue samples were collected from 3 mice per group at predose, 1, 2, 3, 6, 8, 12, 18, and 24 h postdose. Plasma (separated from whole blood collected in K2EDTA tubes) and vulvovaginal tissue were stored frozen until analysis. Vaginal lavage fluid was collected with a solution of phosphate-buffered saline (PBS)-0.2% tocopherol polyethylene glycol succinate (TPGS) (to mitigate nonspecific binding to pipette tips and collection vials), centrifuged to produce supernatant, and frozen until analysis.

All samples were extracted via protein precipitation. Vaginal lavage fluid samples were corrected for dilution based on blood urea levels (18). Calculated concentrations for all samples were interpolated from matrix-matched calibration curves using Applied Biosystems Analyst 1.4.2 software. Standard curves were created by generating least-squares fitting plots of peak area ratio (analyte peak area divided by internal standard peak area) versus nominal concentration. Incurred sample concentrations were calculated from results of least-squares fits.

**MIC testing of clinical trial isolates.** Susceptibility testing was performed using a broth microdilution method according to CLSI M27-A4 guidelines (5). RPMI 1640 with morpholinepropanesulfonic acid (MOPS) was the medium for all testing, and the inoculum size was $0.5 \times 10^3$ to $2.5 \times 10^3$ CFU/ml. MIC endpoints for IBX were recorded at 50% inhibition, compared to those of the growth control, after 24 h incubation. MICs of the comparators FLU (Sigma-Aldrich) and MICA (Astellas Pharma) were recorded at 50% inhibition following 24 h of incubation.

**MIC testing at various pH levels.** IBX (Scynexis, Inc.) and MICA (Astellas Pharma) were tested in a range of 0.015 to 8 $\mu$g/ml, while FLU (Sigma-Aldrich) was tested in a range of 0.125 to 64 $\mu$g/ml. Serial dilutions of each antifungal were prepared in RPMI 1640 (USBiological) at three different pH levels; pH 7, pH 5.72, and pH 4.5. Adjustments in pH were made using sodium hydroxide or hydrochloric acid, with buffering by morpholinepropanesulfonic acid (MOPS) (0.165 M) as described by Marr et al. (7).

Ten strains each of *C. albicans* and *C. glabrata* were obtained from recent clinical trial patients with vulvovaginal candidiasis (VVC) prior to treatment. Inocula of each strain were prepared in RPMI 1640 at each pH level to a concentration of $0.5 \times 10^3$ to $2.5 \times 10^3$ blastospores/ml. Inocula and antifungal dilutions were added to the wells of microtiter plates in equal 100 $\mu$l amounts and incubated at 35°C for 24 h. Wells containing no antifungal served as the growth control. *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were tested concurrently to ensure quality control.

Inhibition endpoints were read visually as a 50% reduction in growth compared to the growth control. Differences in the geometric mean of the MIC values were assessed for significance by analysis of variance (ANOVA) using Tukey's posttest for multiple comparisons.

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