

***In Vitro* Activity of Ibrexafungerp against 187 Fluconazole-susceptible and -resistant *Candida* Species Isolates from Patients with Vaginal Yeast Infections.**

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OBJECTIVES:

1. Learner will understand the activity of ibrexafungerp against *Candida* spp. isolates from VVC patients
2. Learner will observe that resistant mechanisms to fluconazole do not affect the *in vitro* activity of ibrexafungerp
3. Learner will understand that ibrexafungerp may be a future option for treatment of vaginal yeast infections in their clinical practice.

Purpose

- Growing reports in VVC of non-*albicans* species of *Candida*, notably *C. glabrata*, *C. parapsilosis*, and *C. krusei* with intrinsic resistance to the azole drug class.
- Among patients with vulvovaginal candidiasis (VVC), *C. albicans* is the most frequently observed *Candida* species. What is extremely worrisome is the increase in fluconazole (FLU) resistance observed in *C. albicans* vaginal isolates.
- Previous *in vitro* studies have shown a negative effect on the activity of fluconazole in low pH testing environments, pH 4.5.³
- Ibrexafungerp (IBX) is an oral anti-fungal agent that has recently completed two successful phase 3 clinical trials for the treatment of VVC. IBX belongs to a novel class of glucan synthase inhibitors, triterpenoid antifungal, and has shown activity against azole-resistant *Candida* species
 - This study describes the effect of low pH environments on the *in vitro* activity of ibrexafungerp against clinical VVC isolates, including those resistance to fluconazole

Methodologies

- Ibrexafungerp was evaluated *in vitro* against 187 vaginal *Candida* isolates obtained from patients seen at the Wayne State University Vaginitis Clinic.
 - 52 FLU-resistant *C. albicans* (FLU MIC > 2 ug/mL)
 - 30 FLU-sensitive *C. albicans* (FLU MIC < 2 ug/mL)
 - 30 randomly selected *C. glabrata* isolates
 - 25 each randomly selected isolates of *C. krusei*, *C. parapsilosis*, and *C. tropicalis*.
- Susceptibility tests were performed according to CLSI M27-A4 guidelines with the media adjusted to pH 7.0 and pH 4.5; ibrexafungerp MIC readings were conducted at 24 and 48 hrs.

Ibrexafungerp MIC Values Were Not Adversely Affected When Tested at Normal pH (7.0) and Lower pH (4.5)

- Ibrexafungerp demonstrated *in vitro* activity against all the VVC clinical isolates tested at normal pH 7.0 and at pH 4.5 (replicating the acidic environment of the vagina)
- No differences were observed in ibrexafungerp's MIC₉₀ values (24 hr endpoint at pH 7 and pH 4.5) between the FLU resistant and FLU-sensitive *C. albicans* isolates (MIC₉₀ = 0.03 mg/mL).

IBX pH 7.0 MIC (mg/ml)	Flu-R <i>C. albicans</i> (N=52)	FLU-S <i>C. albicans</i> (N=30)	<i>C. glabrata</i> (N=25)	<i>C. krusei</i> (N=25)	<i>C. parapsilosis</i> (N=25)	<i>C. tropicalis</i> (N=25)	IBX pH 4.5 MIC (mg/ml)	Flu-R <i>C. albicans</i> (N=52)	FLU-S <i>C. albicans</i> (N=30)	<i>C. glabrata</i> (N=25)	<i>C. krusei</i> (N=25)	<i>C. parapsilosis</i> (N=25)	<i>C. tropicalis</i> (N=25)
MIC ₅₀	0.03	0.03	0.125	0.5	0.25	0.125	MIC ₅₀	0.03	0.03	0.25	0.25	0.125	0.125
MIC ₉₀	0.03	0.03	0.25	0.5	0.5	0.25	MIC ₉₀	0.06	0.06	0.5	0.25	0.25	0.25
Mode	0.03	0.03	0.125	0.5	0.25	0.25	Mode	0.03	0.03	0.25	0.25	0.125	0.25
Range	0.03 – 0.06	0.03 – 0.06	0.06 – 0.25	0.25 - 1	0.125 - 4	0.03 – 0.25	Range	0.03 – 0.06	0.03 – 0.05	0.125 – 0.5	0.06 – 0.5	0.03 – 0.5	0.03 – 0.5

Implications for Women's Health

- Ibrexafungerp exhibited significant *in vitro* activity against FLU-resistant and FLU-sensitive vaginal *Candida* species isolates.
- Unlike fluconazole, which is highly affected in an acidic pH testing environment, the potent *in vitro* activity of ibrexafungerp was retained at lower pH (4.5), relevant for the vaginal milieu.
- These results suggest that ibrexafungerp is a highly-promising, orally bioavailable, non-azole, antifungal agent for the treatment of VVC and prevention of recurrence VVC.