Phase 3 Oral Ibrexafungerp Study in Vulvovaginal Candidiasis (VANISH-303): Outcomes in Non-*albicans Candida* spp.

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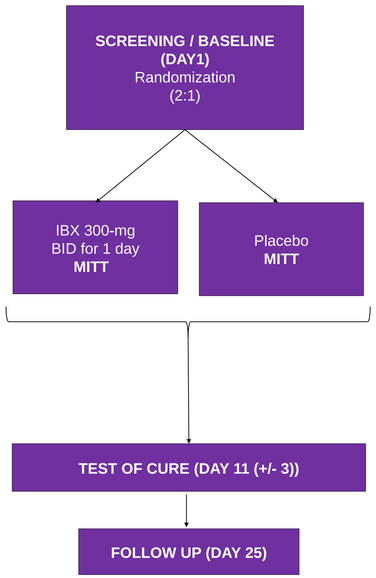
BACKGROUND

Vulvovaginal Candidiasis (VVC) affects 75 million women at least once in their lifetime. The predominant fungal pathogen isolated in VVC is *Candida albicans.* Non-*albicans Candida* (NAC) species vaginal infections are difficult to treat because of their intrinsic and acquired resistance to current oral and topical azoles. Optimal treatments for NAC vaginitis are limited and current recommendations are 7-14 days of intravaginal azole or topical boric acid. Ibrexafungerp (IBX) is a novel oral triterpenoid antifungal in development for the treatment of vulvovaginal candidiasis (VVC). IBX is fungicidal with broad *in vitro* activity against *Candida* spp., including NAC and fluconazole-resistant *Candida*. We present an analysis of outcomes from all subjects and those with NAC VVC from VANISH-303, one of two large Phase 3 studies of IBX in women with VVC.

METHODS

VANISH-303, a multicenter, randomized, double-blind study in the U.S. Patients were randomized to oral IBX 300 mg BID (one-day) or matching placebo in a 2:1 ratio. Eligible patients (ages 12 and over) had to present with an episode of VVC with Vaginal Signs and Symptoms (VSS) score ≥4 (moderate to severe VVC). Primary efficacy population was the modified-intent-to-treat (mITT), patients with culture confirmed *Candida* spp. infection at baseline who received at least one dose of study treatment.

Figure 1: Oral Ibrexafungerp VANISH-303 Study Design



Primary Objectives:

To evaluate the efficacy of oral IBX versus placebo in subjects with VVC by comparing the clinical outcomes of ibrexafungerp and placebo

Primary Endpoint

The primary endpoint was Clinical Cure, defined as complete resolution (VSS=0) at the Day-10 test-of-cure (TOC) visit and patients were followed through Day- 25 follow-up (FU) visit. This TOC endpoint is more stringent than the endpoint of VSS≤2 as observed in many previous VVC trials in the literature.

RESULTS

VANISH-303 study included 286 subjects in the mITT group, 188 subjects in the IBX arm and 98 in the placebo arm. Of these, 19 subjects in the IBX arm and 13 subjects in the placebo arm had a NAC isolate at baseline. Five patients had co-infection with two *Candida* spp. Isolates at baseline in the IBX arm with *C. glabrata* being the most common NAC isolate. In the MITT group the Clinical Cure at TOC for IBX was 50.5%, superior (p=0.001) to placebo, 28.6%. In the NAC group the clinical cures (TOC) were 42.1% for IBX and 30.8% for placebo.

Table 1: Patient Demographics

mITT	VANISH-303 IBX 300mg BID (N=188) n (%)
Age, Median (Min,Max)	32.5 (18, 67)
Race % White | % Black or African American	54.8 | 38.8
Body Mass Index (kg/m^2) Median (Min, Max) Percent BMI > 35	28.3 (18, 62) 23.4
Diabetes Mellitus	18 (9.6)

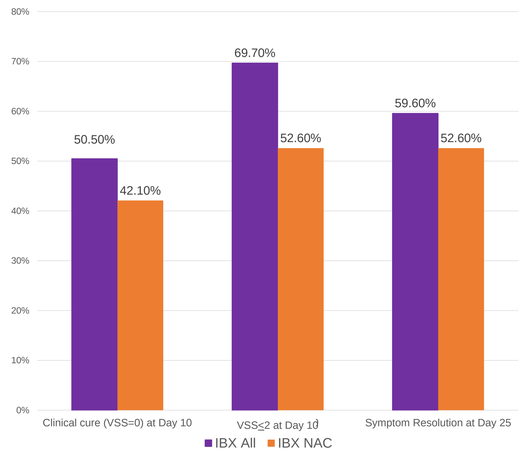
Table 2: VANISH-303 Efficacy Endpoints

mITT	IBX ALL 300mg BID (N=188) n (%)	IBX NAC 300mg BID (N=19) n (%)
Clinical Cure (S&S=0) at TOC (Day 11)	95 (50.5)	8 (42.1)
Mycological eradication at TOC	93 (49.5)	4 (21.1)
Clinical Improvement (S&S≤1) at TOC	121 (64.4)	9 (47.4)
Symptom Resolution at FU (Day 25)	112(59.6)	10 (52.6)

Table 3: Subject pathogens isolated at baseline

Pathogen	Ibrexafungerp n (%)
C. albicans	173 (92)
Non-*albicans Candida* total	19 (10.1)
C. albicans / C. glabrata	4 (2.1)
C. albicans / C. lusitaniae	1 (0.5)
C. glabrata	7 (3.7)
C. tropicalis	4 (2.1)
C dubliniensis	2 (1)
C. parapsilosis	1 (0.5)

Figure 2: Ibrexafungerp ALL patients (n= 188) and Non-*albicans Candida* Patient Outcomes (n = 19)



Candida isolates from baseline were tested for *in vitro* Minimum Inhibitory Concentration (MIC) for IBX and Fluconazole (FLU). Table 4, shows the range, MIC_{50} and MIC_{90} for 184 *Candida* isolates from the IBX subjects of the study. IBX MIC_{50} and MIC_{90} were lower than FLU for both *C. albicans* and *C. glabrata.*

Table 4: MIC Values for Ibrexafungerp and Fluconazole against *Candida albicans* and *Candida glabrata* Isolates collected at baseline

MIC's for *Candida* Baseline Isolates for IBX and FLU	IBX isolates IBX MIC's	IBX isolates FLU MIC's
Candida albicans (N=173)		
Range (μg/mL)	0.016-0.25	0.12-4
MIC_{50} (μg/mL)	0.06	0.12
MIC_{90} (μg/mL)	0.12	0.5
Candida glabrata (N=11)		
Range (μg/mL)	0.12-1	0.12-32
MIC_{50} (μg/mL)	0.5	4.0
MIC_{90} (μg/mL)	0.5	4.0

Non *albicans Candida* Patient Outcomes

There were a total of 19 subjects (10.1%) with NAC VVC in the IBX arm. Of the 19 subjects, 10 were Black/African American, 9 were White. Median BMI was 34.4 kg/m^2. Figure 2 shows the efficacy outcomes in the IBX arm: 42.1% (8/19) subjects had clinical cures (VSS=0) at Day 10, 52.6% (10/19) subjects had a VSS≤2 at day 10 and 52.6% (10/19) patients had symptom resolution at Day 25.

Safety

Adverse events (AEs) for IBX were predominately gastrointestinal in nature, with diarrhea (25.5%), nausea (16.2%), abdominal pain (6.9%) and vomiting (2.0%), with most being mild to moderate, lasting one day.

CONCLUSIONS

IBX appears to have a clinical activity against NAC, but there were too few subjects with NAC in the study to draw a strong conclusion. Further study is warranted to understand IBX efficacy in NAC. IBX may provide a non-azole treatment option in the future for patients with NAC vaginitis.

For additional information contact SCYNEXIS at info@scynexis.com.