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This activity is supported by an educational grant from SCYNEXIS, Inc.

Audience: This activity was designed for OB/GYN physicians, advanced practitioners in women's health and primary care providers in women's health

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

- Appreciate the scope of the problem of *Candida* infection in terms of cost, lost productivity, and medical visits
- Learn current diagnostic and treatment patterns for vulvovaginal candidiasis
- Appreciate the attributes of the new antifungal class (triterpenoids) for vulvovaginal candidiasis
- Analyze clinical trial data with the non-azole approach to vulvovaginal candidiasis

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CONFLICT OF INTEREST DISCLOSURE

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SUPPLEMENT TO
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A New Approach to an Old Problem: Not Just the Azoles for Vulvovaginal Candidiasis

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As virtually all health care providers are aware, symptoms of vulvovaginal candidiasis (VVC) are commonly reported among many of our patients. Consider the following statistics:

- 75% of all women experience at least 1 episode of VVC during their lifetime[1]
- 45% of women will have 2 to 5 episodes of VVC in their lifetime[2]
- In the United States, there are 10 million office visits for vaginal symptoms, of which 20% to 25% are for *Candida* infections[3]
- Until recently, the azole family of drugs was the predominant treatment indicated for VVC[4]
- The majority of women prefer oral therapy to topical/intravaginal therapy[5]

The microbiology of VVC is becoming better understood. *Candida albicans* is responsible for 80% to 90% of VVC,[1] with non-*albicans Candida* responsible for the other 10% to 20% of VVC. Additionally, such non-*albicans Candida* is found in approximately 40% of recurrent infections, versus 10% to 20% of acute infections[6]; although asymptomatic *Candida* colonization has been found in 20% to 30% of all women.[7] In 2015, the Centers for Disease Control and Prevention (CDC) reported that 7% of *Candida* infections are resistant to fluconazole treatment.[4]

The burden on patients is quite large: $4.7 billion in lost productivity[2] resulting from approximately 33 work hours lost per year,[8] and an estimated 1.4 million outpatient visits annually in the United States.[9] VVC may be uncomplicated or complicated. Uncomplicated disease presents with mild to moderate symptoms, occurs sporadically and is usually caused by *C albicans* or another non-*albicans Candida* which are sensitive to most antifungal medications. Complicated disease may be severe, recurrent, or caused by a *Candida*

TABLE 1 Comparison between ibrexafungerp and fluconazole

	Ibrexafungerp[10]	Fluconazole[11]
Mechanism of action	Glucan synthase inhibitor	14α-demethylase inhibitor
Cidal/static vs *Candida*	Fungicidal	Fungistatic
Active vs azole-resistant *Candida*	Yes	No
Activity impacted at low vaginal pH	No[12]	Yes[12]
Vaginal tissue/plasma ratio	9:1[1]	1:1[13]
Evidence of QTc prolongation	No	Yes
Evidence of liver toxicity	No	Yes
One-day oral dosing	Yes	Yes

species that is resistant to some of the commonly used antifungal medications.

Treatment options for VVC may be oral or vaginal. Most antifungals for VVC are azoles (eg, fluconazole, terconazole, miconazole, clotrimazole, itraconazole) and women who are allergic to one of them may also be allergic to the others. An increasing number of *C albicans* infections and many infections caused by non-*albicans Candida*, such as *C glabrata*, *C dubliniensis*, and *C krusei*, are fluconazole resistant.[14] In some cases, these resistant infections will respond to vaginal azole medications, yet many are resistant to all of them and require treatment with non-azole medication.

Uncomplicated VVC can be treated with almost any of the available antifungal treatment options including both oral and vaginal medications.[15,16] The choice between oral and vaginal medication is usually based on the balance between the side-effect profile, convenience, and patient preference. The most common side effects of oral medication are gastrointestinal (GI) intolerance and headaches. Vaginal medication avoids GI and most systemic side effects; however, local side effects, such as itching, burning, irritation, and swelling, may be confused with persistent or recurrent infection and may lead to unnecessary retreatment. Also, fluconazole interacts with many other medications, while the use of vaginal medications avoids these drug-drug interactions.

Ibrexafungerp is a first-in-class, oral triterpenoid (non-azole) antifungal that is administered for 1 day. Unlike azole antifungals, which only inhibit fungal growth, ibrexafungerp is fungicidal.[1,17] Since it is not an azole, it can be used in those who are allergic to fluconazole or other triazoles and retains its activity against most fluconazole-resistant infections. Compared to fluconazole, ibrexafungerp is readily accumulated in vaginal tissue and secretions following oral administration.[18,19] It also works better at vaginal pH levels[18,12] compared with azole antifungals, which are significantly less effective at lower pH levels[14] **(Table 1)**. The treatment course (300 mg [two 150-mg pills] twice daily for 1 day) and oral, rather than vaginal, administration improves adherence and avoids topical side effects that could be confused with recurrent or resistant disease. Ibrexafungerp is contraindicated in pregnant women.

Comparing the efficacy of ibrexafungerp to fluconazole is difficult because there are no head-to-head studies. The clinical trials of ibrexafungerp were designed and evaluated based on industry guidance released by the US Food and Drug Administration in 2019, which included trial design and efficacy endpoint recommendations, with more stringent definitions of clinical cure (absence of all vulvovaginal signs and symptoms [VSS=0]). This differed from studies previously reported on VVC.[20] The trials also included test-of-cure and follow-up visits, which also differed from some previously published studies.

In phase 3 clinical trials,[21,22] 50.5% to 63.3% of symptomatic patients treated with ibrexafungerp had complete resolution of their symptoms (VSS=0). By comparison, following a single dose of fluconazole, VSS=0 was reported in 47.4% of patients on day 7 and 57.9% on day 14.[23] Using the older definition of clinical cure (VSS $\leq$2), a single dose of fluconazole had a clinical cure rate of 80.9% on day 14 compared with 70% to 76.1% for ibrexafungerp.[18,12] Furthermore, on day 25 following treatment with ibrexafungerp, the percentage of patients with resolution of their symptoms was 59.6% for VSS=0 and 64.4% for VSS $\leq$1[21,22] **(Figure 1)**. By comparison, some previous studies of fluconazole reported an 11% to 20% decrease in sustained response from day 14 to day 35, depending on the number of doses[24] **(Figure 2)**.

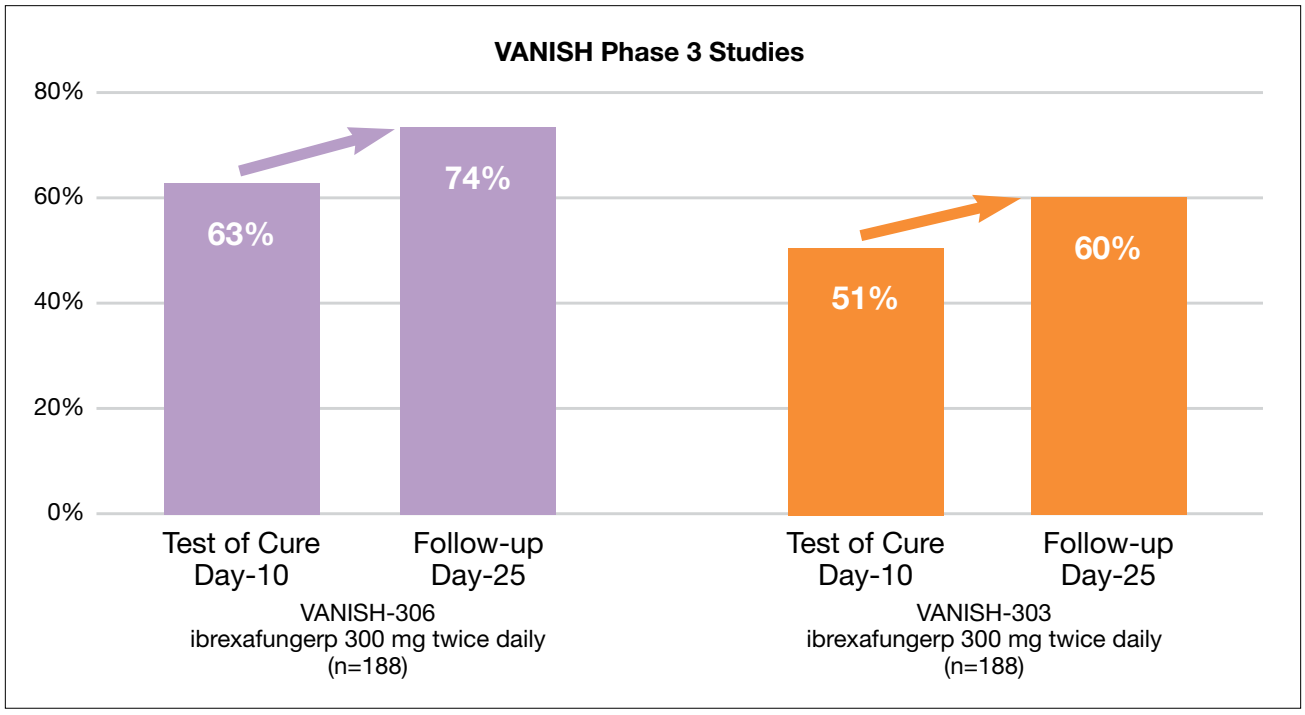

FIGURE 1 Percentage of patients with complete resolution of their symptoms (VSS=0) improved between the initial post-treatment evaluation and day 25.[21,22]

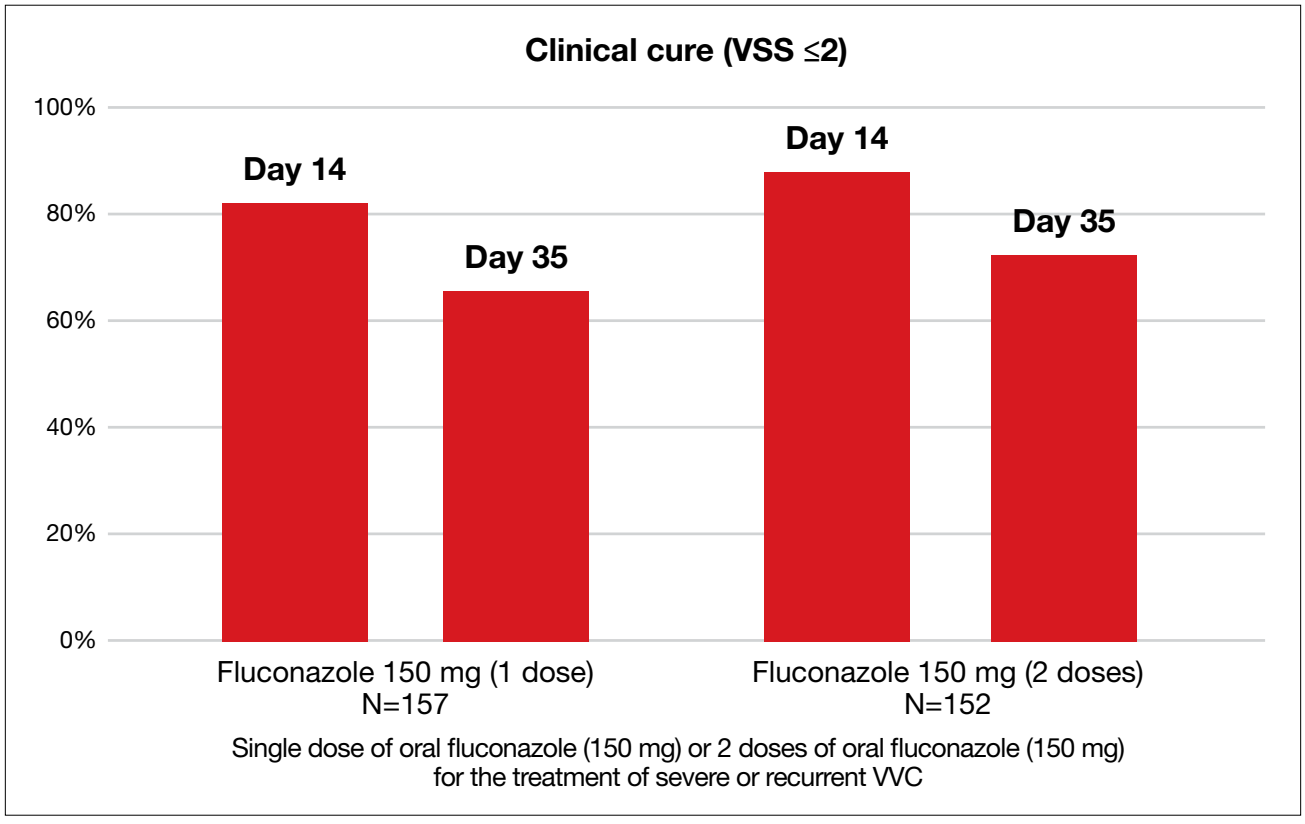

FIGURE 2 Decreased sustained response of fluconazole from days 7 to 14 to days 28 to 35 following treatment.[24]

Some studies have shown that a single dose of fluconazole is not as effective with severe disease (VSS ≥7)[24] and current guidelines recommend oral fluconazole every 3 days for 2 to 3 doses for severe VVC.[25] Conversely, in the ibrexafungerp studies, the median VSS score to be considered severe was VSS=9-10, where no loss of clinical effectiveness was found after a 1-day dose.[21,22]

The majority of adverse events reported were GI related and were mild to moderate in severity. These included diarrhea, nausea, abdominal pain, abdominal discomfort, and dizziness.

In summary, while fluconazole remains an effective and inexpensive treatment option for the majority of women with uncomplicated VVC, more severe disease requires treatment over several days. Also, some *Candida* species, such as *C glabrata*, are fluconazole resistant and there is increasing emergence of fluconazole-resistant *C albicans*. Ibrexafungerp, as a single-day, oral, non-azole antifungal, has an important role in treating patients with severe or recurrent disease and those with fluconazole-resistant *Candida*. Ibrexafungerp is fungicidal rather than fungistatic. It is not an azole, so it can be used in those who are allergic to fluconazole or other triazoles, and it retains its activity against most fluconazole-resistant infections. It has no hepatotoxicity and fewer drug-drug interactions. Although there are no head-to-head comparisons with fluconazole, and comparison to older studies is difficult because the definitions of clinical response have changed, the long-term efficacy of ibrexafungerp appears to be superior to that of fluconazole. ●

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