Riding the Wave of Change in Managing Vulvovaginal Candidiasis—Adapting to a New Era

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Learning Objectives

After participating in this educational activity, participants should be better able to:

- Describe the symptoms, exam findings, and diagnostic testing for vulvovaginal candidiasis (VVC)
- Define the criteria by which VVC infections are categorized as "uncomplicated" or "complicated"
- Describe advantages/limitations of existing and novel therapeutic interventions for VVC

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Epidemiology

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Prevalence of VVC and RVVC

70%

Worldwide prevalence of VVC

10% of whom suffer from recurrent VVC (RVVC)

138 million = number of women affected annually

372 million = number affected by RVVC during their lifetime

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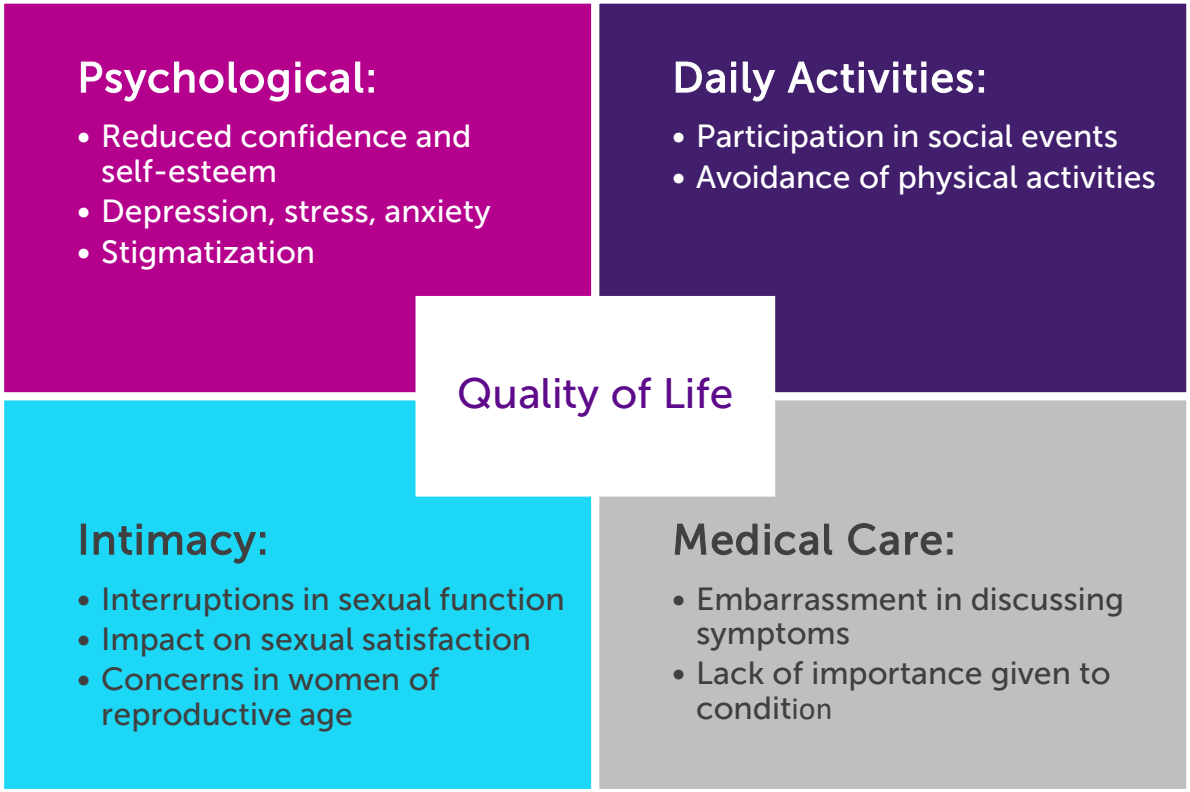
Denning DW, et al. *Lancet Infect* Dis. 2018;18(11):e339-e347.

RVVC: Impact on Daily Life



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Challenges with VVC and RVVC

Diagnosis

- Use of correct diagnostic tests
- No ICD-10 code for RVVC

Awareness

- Under-recognition
- Trivialization of the disease
- Differentiating from acute episodic VVC

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- Incorrect use of OTC treatments
- Discomfort discussing symptoms

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Management

- No FDA-approved RVVC treatment
- Few treatment options
- Adverse effects and contraindications

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Outcomes

- High recurrence rates
- Lack of adherence to maintenance therapy

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Diagnostic Tests

Microscopy:

- In-office results
- 40%-70% sensitivity
- Frequent overdiagnosis and underdiagnosis

Culture:
required when microscopy is negative and vaginal pH within normal range (4.0-4.5)

- Results may take days to weeks
- Identifies species
- May be limited by pre-treatment
- Recommended: resistance testing or recurrent/refractory disease
- Current gold standard

Advanced testing:
DNA probe and PCR

- DNA probe: results within hours; lower sensitivity
- PCR: commercial labs; results within days; higher sensitivity
- Availability limited in some healthcare settings
- May miss certain species of yeast

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Sobel JD. *Am J Obstet Gynecol*. 2016;214(1):15-21; Committee on Practice Bulletins—Gynecology. *Obstet Gynecol*. 2020;135(1):e1-e17.

Pathophysiology

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Pathophysiology: Sporadic VVC vs RVVC

1

Asymptomatic colonization

Yeast from lower GI tract migrates to vagina

Stage may persist for years

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Pathophysiology: Sporadic VVC vs RVVC

1

Asymptomatic colonization

Yeast from lower GI tract migrates to vagina

Stage may persist for years

2

Sporadic VVC

Genetic predisposition

Trigger-based yeast overgrowth

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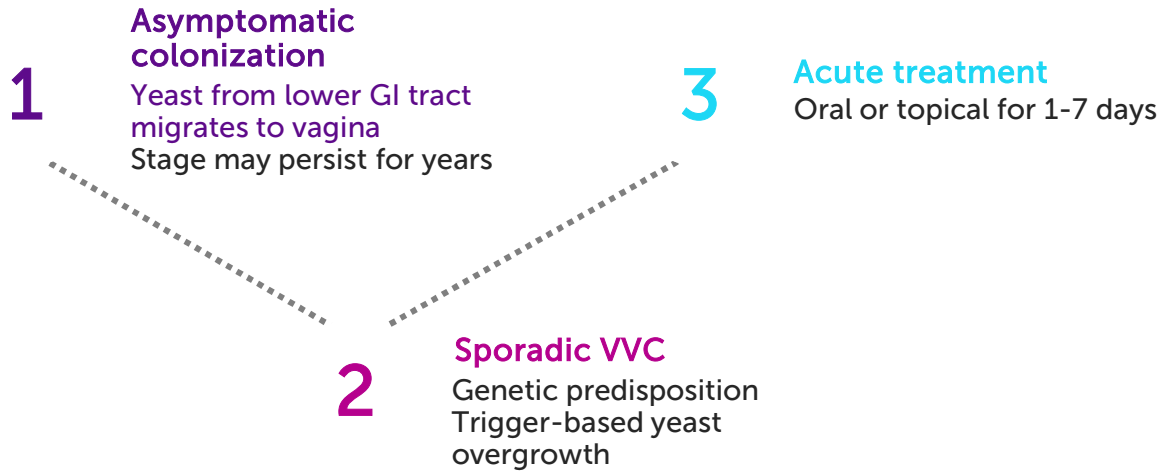
Pathophysiology: Sporadic VVC vs RVVC



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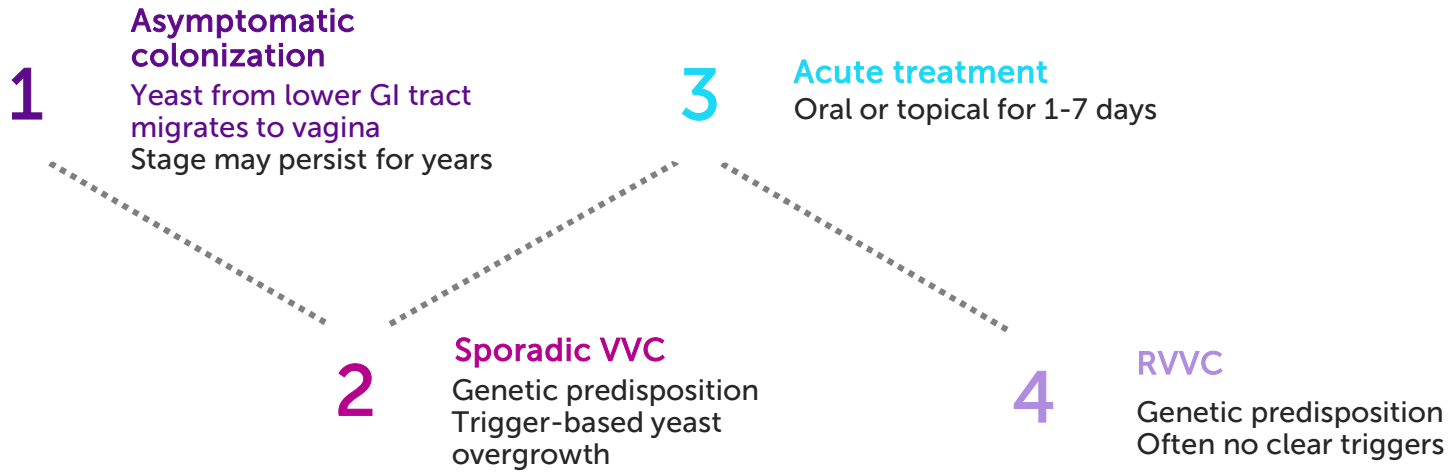

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Pathophysiology: Sporadic VVC vs RVVC

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Stage may persist for years

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Sporadic VVC

Genetic predisposition

Trigger-based yeast overgrowth

3

Acute treatment

Oral or topical for 1-7 days

4

RVVC

Genetic predisposition

Often no clear triggers

5

Maintenance treatment

Long-term fluconazole (6 months)

40%-50% recur within 6 months of discontinuation

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Denning DW, et al. *Lancet Infect Dis*. 2018;18(11):e339-e347.

Sporadic VVC vs Recurrent VVC

	Sporadic	Recurrent
Frequency	• Infrequent	• Chronic disease • Defined as ≥3 episodes/year
Triggers	• Prior history: antibiotics, intercourse, diabetes, estrogen • Avoiding triggers may help	• Same as sporadic; often no triggers or modifiable risk factors • Genetic predisposition more relevant
Treatment	• Multiple treatments approved • Short term: 1 to 7 days, depending on severity	• No FDA-approved treatments • Long term: ≥6 months of weekly, oral fluconazole
Outcomes	• Resolution of acute symptoms	• Resolution of acute symptoms • ≥50% recurrence within 6 months

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Denning DW, et al. *Lancet Infect Dis*. 2018;18(11):e339-e347. Pappas PG, et al. *Clin Infect Dis*. 2016;62(4):e1-e50. Sobel JD. *Am J Obstet Gynecol*. 2016;214(1):15-21. Yano J, et al. *BMC Womens Health*. 2019;19(1):48.

Current Treatments

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Current Approved Treatments for Acute VVC

Topical

- Miconazole
- Terconazole
- Clotrimazole
- Tioconazole
- Butoconazole

Oral

- Fluconazole
- Ibrexafungerp*

*Approved by FDA June 2, 2021; not yet updated in guidelines.

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Rationale for Selecting Therapy

UNCOMPLICATED

- Infrequent / sporadic
- Usually *C. albicans* infection
- Mild to moderate symptoms
- Immunocompetent host

COMPLICATED

- Non-*albicans* species infection
- Severe signs and symptoms
  - Erythema
  - Excoriation
  - Fissure
  - Edema
- Recurrent
- Host with complications
  - Uncontrolled diabetes
  - HIV
  - Immunosuppressed host

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Pappas PG, et al. *Clin Infect Dis*. 2016;62(4):e1-e50. Committee on Practice Bulletins—Gynecology. *Obstet Gynecol*. 2020;135(1):e1-e17. Workowski KA, et al. *MMWR Recomm Rep*. 2021;70(4):1-187.

Guidelines for the Treatment of VVC

UNCOMPLICATED

Treatment:

Topical agent x 1-5 days

- or -

Fluconazole 150 mg
po x 1 dose

COMPLICATED

Treatment:

Topical agents x 5-7 days (IDSA);
7-14 days (CDC);
10-14 days (ACOG)

- or -

Fluconazole 150 mg po every
72 hours x 2-3 doses

Followed by maintenance:
Fluconazole 150 mg weekly x 6
months

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ACOG, American College of Obstetricians and Gynecologists; CDC, Centers for Disease Control and Prevention; IDSA, Infectious Disease Society of America.

Pappas PG, et al. *Clin Infect Dis*. 2016;62(4):e1-e50; Committee on Practice Bulletins—Gynecology. *Obstet Gynecol*. 2020;135(1):e1-e17; Workowski KA, et al. *MMWR Recomm Rep*. 2021;70(4):1-187.

Challenges with Fluconazole Treatment

Resistance

- Increasing reports of antifungal resistance
  - Non-*albicans* species
  - More recently even with *C. albicans*

Tolerability

- Alopecia
- Liver and cardiac toxicities (rare)
- Drug-drug interactions (rare)
- Contraindicated in all trimesters of pregnancy
  - Possible cardiac defects

Outcomes

- All VVC may recur following discontinuation of maintenance treatment

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Focus on Ibrexafungerp

STATUS: Approved by FDA on June 2, 2021, as the first and only oral non-azole treatment for vaginal yeast infections.

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Ibrexafungerp (Brexafemme™)

- First-in-class triterpenoid
- Glucan synthase inhibitor
  - Unique binding site from echinocandins (with some overlap)
  - Potential for fewer drug-drug interactions than fluconazole
- Oral bioavailability 35%-51%
  - Greater absorption with high-fat foods
- Half-life 20-30 hours
- Higher levels of penetrations into vaginal tissues
  - 1:9 plasma to vaginal tissue concentration
- Completed phase 2 trials for acute VVC
- Phase 3 trials ongoing for both VVC and RVVC

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Jimenez-Ortigosa C, et al. *Antimicrob Agents Chemother*. 2017;61(9):e00833-17. doi:10.1128/AAC.00833-17; Davis MR, et al. *Med Mycol*. 2020;58(5):579-592.

Ibrexafungerp: Comparisons to Fluconazole

	Ibrexafungerp	Fluconazole
Mechanism of action	Glucan synthase inhibitor	14-α-demethylase inhibitor
Cidal/Static vs *Candida*	Fungicidal	Fungistatic
Active vs azole-resistant spp.	Yes	No
Activity impacted by low vaginal pH	No	Yes
Vaginal tissue/plasma ratio	9:1	1:1
Evidence of fetal toxicity	No*	Yes
Evidence of QTC prolongation	No	Yes
Evidence of liver toxicity	No	Yes
Single-day dosing	Yes	Yes

* At preclinical stages.

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Ibrexafungerp: Phase 2b DOVE Study
Rates of Clinical Cure at Day 10 and Day 25

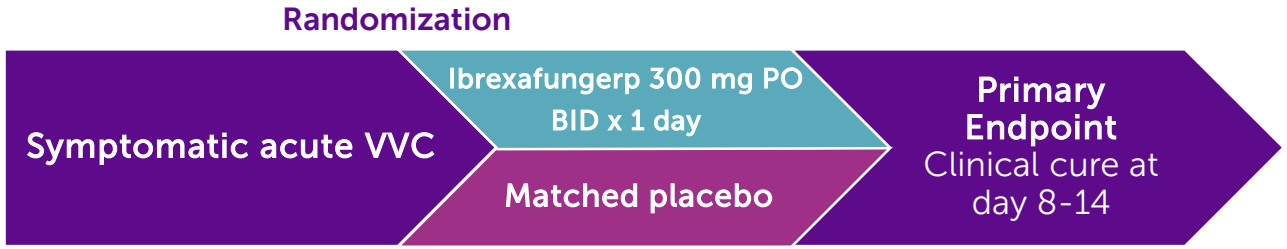
- Randomized, multicenter, double-blind, active-controlled, dose-finding study; evaluated efficacy and tolerability of oral ibrexafungerp vs fluconazole
- Women with moderate to severe acute VVC
  - Primary goal: clinical cure
- Generally safe and well tolerated
- No serious adverse events or discontinuations
- No drug-related serious adverse events in any treatment arm
- Higher incidence of mild to moderate GI events of short duration: nausea, diarrhea, abdominal pain

Rate of Mycological Eradication	Ibrexafungerp 300 mg bid x 1 day	Fluconazole 150 mg x 1 dose
Day 10	63%	63%
Day 25	48%	38%

Cadet R, et al. *Obstet Gynecol*. 2019;133:113S-114S.

Ibrexafungerp: Phase 3 Trials for Acute VVC

VANISH 303 and 306: Identical randomized, multicenter, double-blind, placebo-controlled studies of females aged ≥12 years with symptomatic acute VVC. VANISH 303 completed Sept 2019; VANISH 306 ongoing as of March 2021.



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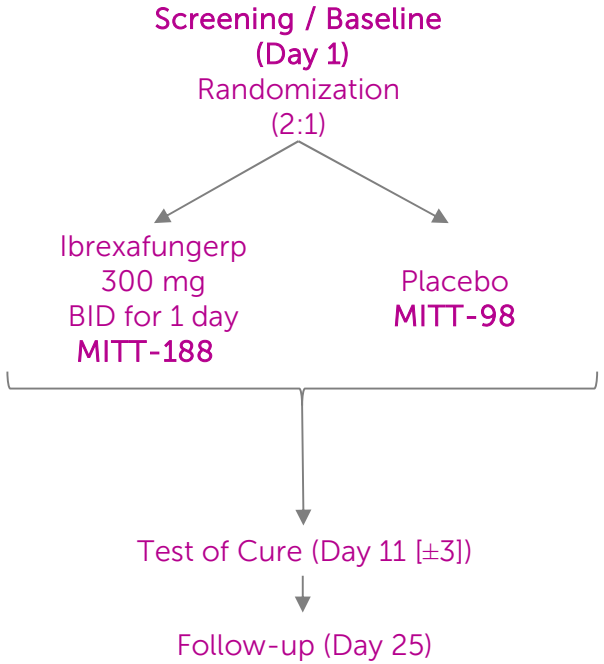
VANISH-303: Ibrexafungerp Acute VVC Phase 3 Study

- Inclusion criteria
  - Vaginal Signs and Symptoms Standardized Scale ≥ 4*
  - Age ≥ 12 years
  - KOH+
- Primary study population
  - MITT = subset of ITT population with a positive culture at baseline



* Vaginal Signs and Symptoms Standardized Scale ranges from 0 to 18. Vaginal signs = edema, erythema, excoriation; vaginal symptoms = itching, burning, irritation. Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

Schwebke J, et al. Abstract presented at IDSOG; 2020.

VANISH-303: Endpoints

- Primary endpoint
  - Percentage of subjects with clinical cure (complete resolution of signs and symptoms) at the test-of-cure (TOC) site
- Key secondary endpoints
  - Percentage of subjects with mycological eradication (negative culture for growth of *Candida* species) at the TOC visit
  - Percentage of subjects with clinical improvement (partial or complete resolution of signs and symptoms with total composite score no greater than 1 at the TOC site)
  - Percentage of subjects with complete resolution of symptoms at follow-up (Day 25) visit
- Safety and tolerability

Schwebke J, et al. Abstract presented at IDSOG; 2020.

VANISH-303: Demographics and Baseline Characteristics

MITT	VANISH-303	
	Ibrexafungerp 300 mg BID N = 188 n (%)	Placebo N = 98 n (%)
Age, Median (Min | Max)	32.5 (18 | 67)	34 (17 | 66)
Race % White | % Black or African American	54.8 | 38.8	54.1 | 43.9
Body Mass Index (kg/m^2) Median (Min | Max) Percent BMI > 35	28.3 (18 | 62) 23.4	29.1 (17 | 54) 22.4
Diabetes Mellitus	18 (9.6)	8 (8.2)
Baseline pathogen (more than 1 baseline isolate was reported in some cases)		
Candida albicans	173 (92)	90 (91.8)
Candida glabrata	11 (5.9)	11 (11.2)
Candida tropicalis	4 (2.1)	1 (1)

Schwebke J, et al. Abstract presented at IDSOG; 2020.

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VANISH-303: Efficacy Endpoints

MITT	Ibrexafungerp 300 mg BID N = 188 n (%)	Placebo N = 98 n (%)	OR (95 % CI) *P* value
Clinical Cure (S&S = 0) at TOC (Day 11)	95 (50.5)	28 (28.6)	1.71 (1.20, 2.43) 0.001
Mycological eradication at TOC	93 (49.5)	19 (19.4)	2.87 (1.80, 4.57) <0.001
Clinical Improvement (S&S ≤ 1) at TOC	121 (64.4)	36 (36.7)	1.77 (1.31, 2.38) <0.001
Symptom Resolution at FU (Day 25)	112 (59.6)	44 (44.9)	1.41 (1.07, 1.85) 0.009

Schwebke J, et al. Abstract presented at IDSOG; 2020.

VANISH-303: Safety

Safety Set	Ibrexafungerp 300 mg BID N = 247 n (%)		Placebo N = 124 n (%)	
Subjects with TEAE	185 (74.9)		76 (61.3)	
Subjects with severe TEAE*	3 (1.2)		5 (4.0)	
TEAEs leading to drug discontinuation	0		0	
Number of subjects with SAE**	1		2	
Number with drug-related SAE	0		0	
GI Adverse Events	n (%)	% Mild / Severe	n (%)	% Mild / Severe
Diarrhea	63 (25.5)	70 / 0	8 (6.5)	75 / 0
Nausea	40 (16.2)	85 / 2.5	7 (5.6)	75 / 0
Abdominal pain	17 (6.9)	88 / 0	3 (2.4)	100 / 0
Vomiting	5 (2.0)	60 / 0	0	N/A

***Severe TEAE**
****SAEs underlined**

Ibrexafungerp: pneumonia, nausea, bronchial hyperactivity
Placebo: DM, hypokalemia, vulvar erosion, pharyngeal erythema, vestibular disorder

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Schwebke J, et al. Abstract presented at IDSOG; 2020.

Focus on Oteseconazole

STATUS: Investigational. FDA has accepted the Priority Review of New Drug Application for oteseconazole for the treatment of recurrent vulvovaginal Candidiasis. The PDUFA target is early 2022, pending full FDA approval.

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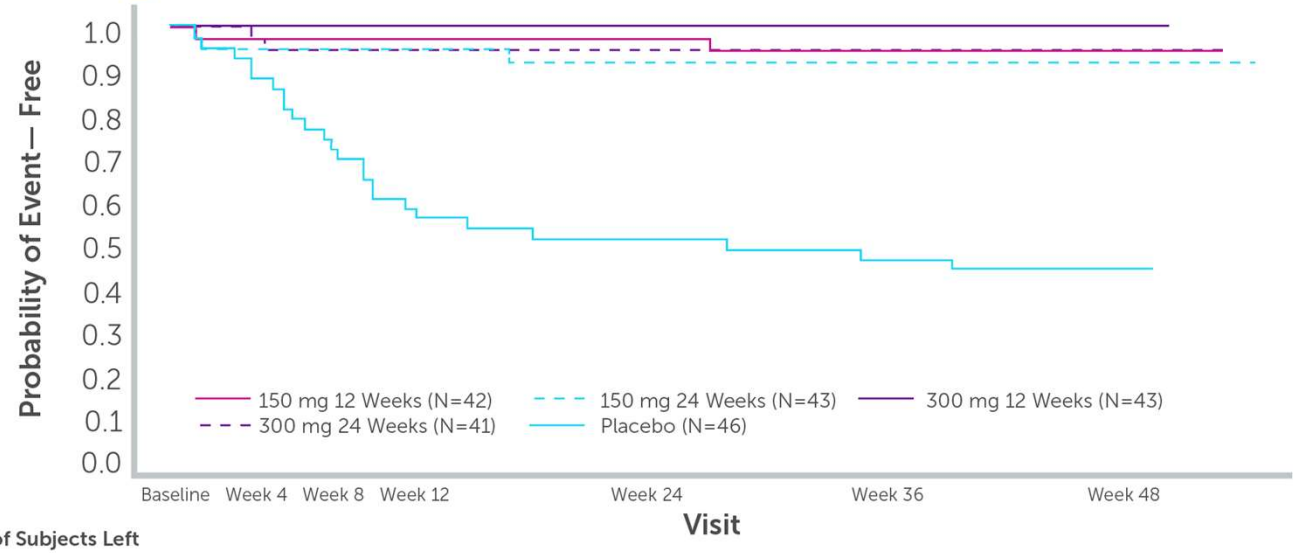
The REVIVE Study: Oteseconazole (VT-1161)

- Phase 2b dose-ranging study
  - Randomized, multicenter, double-blind, placebo-controlled
- 176 women 18-64 years of age completed the trial
  - RVVC (≥3 episodes/year)
  - Severe symptoms
- Initial acute treatment of fluconazole 150 mg q 72 hours x 3 doses
- Then randomized to *(looking for maintenance dose and duration):*
  - Oteseconazole 150 mg daily x 7 days, then weekly x 11 weeks, then once-weekly dose of placebo for 12 weeks
  - Oteseconazole 150 mg daily x 7 days, then weekly x 23 weeks
  - Oteseconazole 300 mg daily x 7 days, then weekly x 11 weeks, then once-weekly dose of placebo for 12 weeks
  - Oteseconazole 300 mg daily x 7 days, then weekly x 23 weeks
  - Matching placebo regimen for 24 weeks

Brand SR, et al. *Am J Obstet Gynecol*. 2018;218(6):624.e1-624.e9.

The REVIVE Study: Time to First Recurrence (ITT Population)



Number of Subjects Left							
150 mg 12 Weeks	42	38	38	37	36	34	12
150 mg 24 Weeks	43	38	38	34	31	30	14
300 mg 12 Weeks	43	38	38	38	37	34	14
300 mg 24 Weeks	41	37	35	35	34	34	16
Placebo	46	38	31	25	22	20	9

Median time to first recurrence:

- Placebo: 28 weeks
- Oteseconazole: Not reached due to low number of recurrences

Brand SR, et al. *Am J Obstet Gynecol*. 2018;218(6):624.e1-624.e9.

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The REVIVE Study: Safety Outcomes

- Most common treatment-emergent adverse effects (≥5% of subjects)
  - Urinary tract infection
  - Bacterial vaginosis
  - Sinusitis
  - Headache
  - Upper respiratory tract infection
  - Nausea
- No drug-related serious adverse events in any treatment arm

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Brand SR, et al. *Am J Obstet Gynecol*. 2018;218(6):624.e1-624.e9.

RVVC Investigational Studies

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Ibrexafungerp: Phase 3 Trial for Acute RVVC

CANDLE: Randomized, multicenter, double-blind, placebo-controlled study, N = 320 women with RVVC. Granted FDA Special Protocol Assessment. Estimated study completion Sept 2021.

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The VIOLET Study: Oteseconazole (VT-1161)

- Phase 3 Study – results presented at IDSOG 2021 meeting
  - Two parallel randomized, multicenter, double-blind, placebo-controlled studies
  - >600 women 18-64 years of age with ≥3 episodes/year RVVC enrolled
- Oteseconazole protected >90% of participants from a recurrence during the 12-week maintenance and 36-week follow-up phases, compared to approximately 40% of the control group
- Oteseconazole was generally safe and well tolerated, with no drug-related severe adverse events reported
- Study investigators concluded that oteseconazole oral dosing was effective in the treatment of RVVC and prevention of recurrence of acute VVC episodes during maintenance through Week 48

Sobel JD, et al. IDSOG 2021 annual meeting.

Oteseconazole: Ongoing Phase 3 Trials for RVVC

VIOLET: open-label acute treatment with fluconazole followed by oteseconazole vs placebo

ultraVIOLET: oteseconazole vs fluconazole for both acute and maintenance treatment

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Advantages of Ibrexafungerp and Oteseconazole Over Fluconazole

Ibrexafungerp and Oteseconazole vs Fluconazole

Pharmacokinetics

- Long half-lives
- High concentrations in vaginal tissue

Antifungal Resistance

- Increased potency against *Candida* spp. resistant to fluconazole

Tolerability

- Less potential for drug-drug interactions

Outcomes

- Higher number of recurrence-free rates vs fluconazole
- Ongoing phase 3 trials in acute VVC and RVVC

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Key Takeaways

- RVVC is not a trivial disease
- The mainstay of treatment, maintenance fluconazole, has been the same for about 30 years
- Both ibrexafungerp and oteseconazole have unique qualities
- Initial data suggest that they both may represent a significant step forward in managing a challenging infection

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