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

Jack D. Sobel, MD

omnia EDUCATION

1

Faculty Information

Jack D. Sobel, MD
Professor of Medicine
Wayne State University
School of Medicine
Detroit, MI

Consulting Fees: Mycovia Pharmaceuticals, SCYNEXIS
Royalty: Up-To-Date

omnia EDUCATION

2

Learning Objectives

- 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

omnia EDUCATION

3

Epidemiology

omnia EDUCATION

4

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

omnia EDUCATION

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

5

RVVC: Impact on Daily Life

Psychological:
- Reduced confidence and self esteem
- Depression, stress, anxiety
- Stigmatization

Daily Activities:
- Participation in social events
- Avoidance of physical activities

Quality of Life

Intimacy:
- Interruptions in sexual function
- Impact on sexual satisfaction
- Concerns in women of reproductive age

Medical Care:
- Embarrassment in discussing symptoms
- Lack of importance given to condition

omnia EDUCATION

Denning DW, et al. *Lancet Infect Dis*. 2018;18(11):e339-e347; Moshfeghy Z, et al. *J Turk Ger Gynecol Assoc*. 2020;21(2):90-96.

6

Precipitating Factors/Triggers for VVC

- Genetic predisposition
- Precipitating triggers
  - Prior use of antibiotics
  - Diabetes
  - Obesity
  - Use of corticosteroids
  - Pregnancy
  - Immunosuppressive therapy or immunocompromised patients
  - Estrogen therapy
    - > Oral contraceptives
    - > Hormone replacement therapy

omnia EDUCATION

Denning DW, et al. *Lancet Infect Dis*. 2018;18(11):e339-e347; Moshfeghy Z, et al. *J Turk Ger Gynecol Assoc*. 2020;21(2):90-96.

Challenges with VVC and RVVC

Diagnosis

- Use of correct diagnostic tests
- No ICD10 code for RVVC

Awareness

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

omnia EDUCATION

Challenges with VVC and RVVC

Diagnosis

- Use of correct diagnostic tests
- No ICD10 code for RVVC

Self-Treatment

- Incorrect use of OTC treatments
- Discomfort discussing symptoms

Awareness

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

omnia EDUCATION

9

Challenges with VVC and RVVC

Diagnosis

- Use of correct diagnostic tests
- No ICD10 code for RVVC

Self-Treatment

- Incorrect use of OTC treatments
- Discomfort discussing symptoms

Awareness

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

Management

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

omnia EDUCATION

10

Challenges with VVC and RVVC

Diagnosis

- Use of correct diagnostic tests
- No ICD10 code for RVVC

Self-Treatment

- Incorrect use of OTC treatments
- Discomfort discussing symptoms

Outcomes

- High recurrence rates
- Lack of adherence to maintenance therapy

Awareness

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

Management

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

omnia EDUCATION

11

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

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

omnia EDUCATION

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

12

Pathophysiology

13

Pathophysiology: Sporadic VVC vs RVVC

Yeast from lower GI tract migrates to vagina
Stage may persist for years

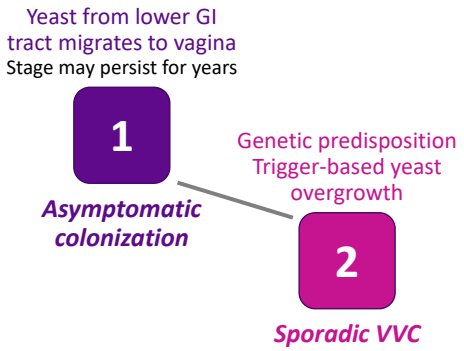
1

Asymptomatic colonization

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

14

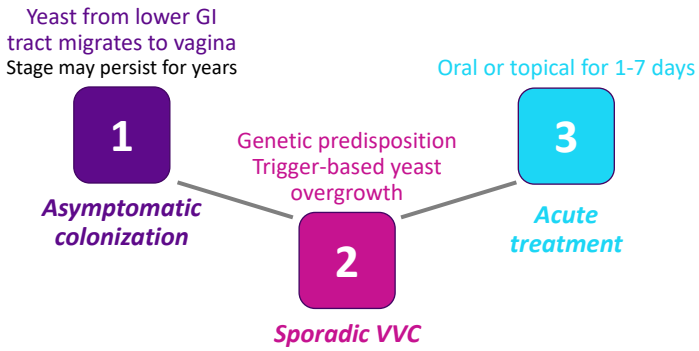
Pathophysiology: Sporadic VVC vs RVVC



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

15

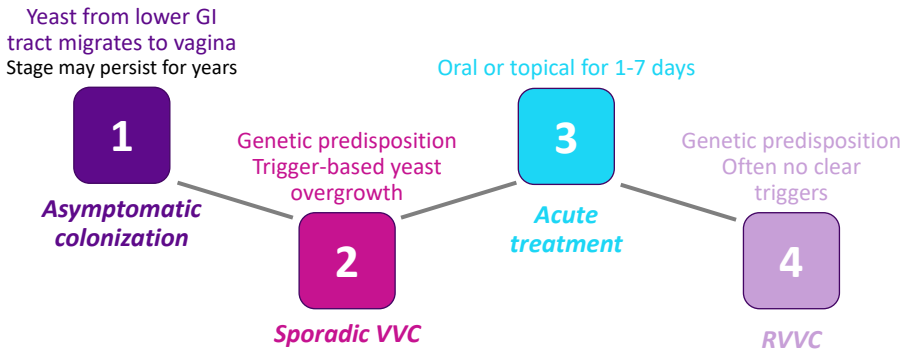
Pathophysiology: Sporadic VVC vs RVVC



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

16

Pathophysiology: Sporadic VVC vs RVVC

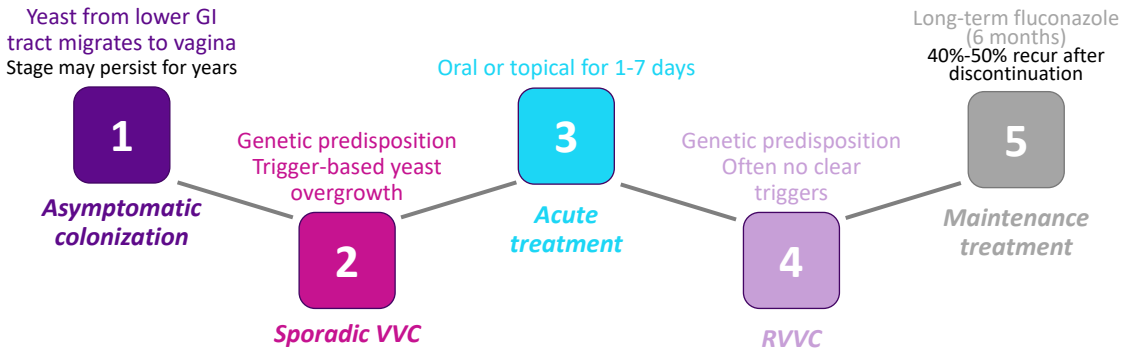


omnia EDUCATION

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

17

Pathophysiology: Sporadic VVC vs RVVC



omnia EDUCATION

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

18

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

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.

omnia EDUCATION

Current Treatments

omnia EDUCATION

Current Treatments for Acute VVC

- **Topical**
  - Miconazole
  - Terconazole
  - Clotrimazole
  - Tioconazole
  - Butaconazole
- **Oral**
  - Fluconazole
  - Itraconazole*

* Not in guidelines.

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

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*. 2015;64(RR-03):1-137.

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

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

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*. 2015;64(RR-03):1-137.

omnia EDUCATION

23

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

Outcomes

- All VVC may recur following discontinuation of maintenance treatment

omnia EDUCATION

24

Investigational Treatments

omnia EDUCATION

25

Oteseconazole (VT-1161)

- Ergosterol synthesis inhibitor
  - Selectively inhibits same CYP51 fungal enzyme as fluconazole but not human enzymes (eg, CYP3A4, CYP2C9, CYP2C19)
  - Potential for fewer drug-drug interactions than fluconazole
- Oral bioavailability 73%
- Half-life >48 hours
- Higher levels of penetrations into vaginal tissues
  - Concentration ≥2-fold greater than plasma
- Granted FDA qualified infectious disease product and fast track designations for RVVC

omnia EDUCATION

Brand SR, et al. *Clin Infect Dis*. 2020;ciaa1204. doi:10.1093/cid/ciaa1204; Warrilow AGS, et al. *Antimicrob Agents Chemother*. 2014;58(12):7121-7127; Garvey EP, et al. *Antimicrob Agents Chemother*. 2015;59(9):5567-5573.

26

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.

omnia EDUCATION

27

The REVIVE Study: Recurrence Rate (ITT Population)

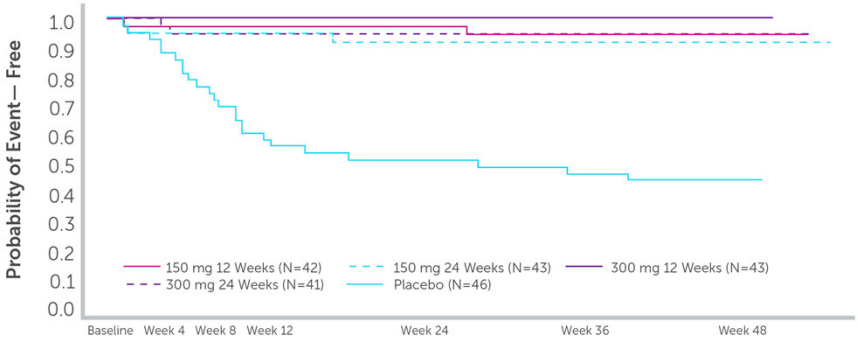
Culture-Verified Acute VVC Episode	Oteseconazole 150 mg/12 wks (n=42)	Oteseconazole 150 mg/24 wks (n=43)	Oteseconazole 300 mg/12 wks (n=43)	Oteseconazole 300 mg/24 wks (n=41)	Placebo (n=46)
N (%)	2 (4.8)	3 (7.0)	0	2 (4.9)	24 (52.2)
95% CI, %	(0.6-16.2)	(1.5-19.1)	(0.0-8.2)	(0.6-16.5)	(36.9-67.1)
Odds ratio	0.0308	0.0414	0.000	0.0438	
P value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	

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

omnia EDUCATION

28

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.

omnia EDUCATION

29

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

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

omnia EDUCATION

30

Oteseconazole vs Fluconazole in Acute VVC: A Phase 2 Study

- Randomized, multicenter, double-blind, placebo-controlled, dose ranging study
- Evaluate the efficacy, safety, and pharmacokinetics of 3 dose levels of oral oteseconazole vs fluconazole
- 55 women with an acute episode of VVC
- Primary goal: cure at 28 days
- Randomized to:
  - Oteseconazole 300 mg qd (75.0%) for 3 days
  - Oteseconazole 600 mg qd (85.7%) for 3 days
  - Oteseconazole 600 mg bid (78.6%) for 3 days
  - Fluconazole 150 mg single dose (per FDA-approved dose)

Brand SR, et al. *Clin Infect Dis*. 2020;ciaa1204. doi:10.1093/cid/ciaa1204

omnia EDUCATION

31

Oteseconazole vs Fluconazole: Cure at 28 Days (ITT Population)

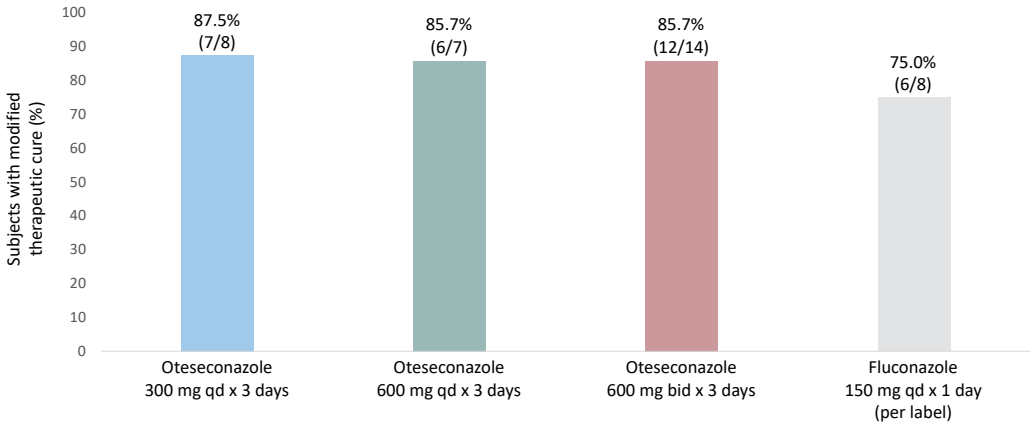
Cure at 28 Days	Oteseconazole 300 mg qd (n=14)	Oteseconazole 600 mg qd (n=12)	Oteseconazole 600 mg bid (n=14)	Fluconazole 150 mg (n=15)
Yes [n (%)]	9 (64.3)	9 (75.0)	11 (78.6)	10 (66.7)
No [n (%)]	5 (35.7)	3 (25.0)	3 (21.4)	5 (33.3)
95% CI	35.1-87.2	42.8-94.5	49.2-95.3	38.4-88.2
P value	0.521	0.496	0.296	

Brand SR, et al. *Clin Infect Dis*. 2020;ciaa1204. doi:10.1093/cid/ciaa1204.

omnia EDUCATION

32

Oteseconazole vs Fluconazole: Modified Therapeutic Cure*



* Modified therapeutic cure = total VVC signs and symptoms severity score of ≤1 and mycological cure at day 28.

Brand SR, et al. *Clin Infect Dis*. 2020;ciaa1204. doi:10.1093/cid/ciaa1204.

omnia EDUCATION

33

Oteseconazole: Ongoing Phase 3 Trials for RVVC

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

Open-label acute treatment for all patients: Fluconazole 150 mg every 72 hours x 3 doses

Randomization

- Oteseconazole 150 mg daily x 7 days then weekly x 11 weeks
- Matched placebo

ultraVIOLET: oteseconazole vs fluconazole for both acute and maintenance treatment

- Oteseconazole 150 mg daily x 2 days → Oteseconazole 150 mg weekly x 11 weeks
- Fluconazole 150 mg every 72 hours x 3 doses → Fluconazole 150 mg weekly x 11 weeks

omnia EDUCATION

34

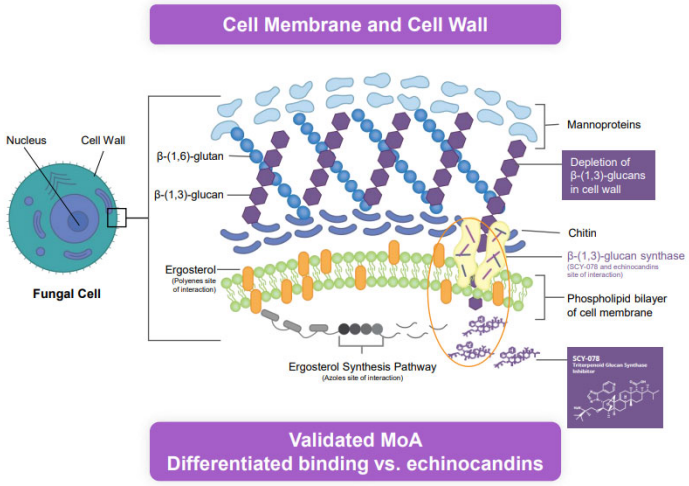
Ibrexafungerp (SCY-078)

- 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

omnia EDUCATION

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: Mechanism of Action



omnia EDUCATION

Larkin E, et al. *Antimicrob Agents Chemother*. 2017;61(5):e02396-e02416. doi:10.1128/AAC.02396-16.

Ibrexafungerp: Comparisons to Fluconazole

	Ibrexafungerp	Fluconazole
Mechanism of action	Glucan synthase inhibitor	14$^{\alpha}$-demethylase inhibitor
Cidal/Static vs *Candida*	Fungicidal	Fungistatic
Active vs azole-resistant spp.	Yes	No
Activity impacted by low vaginal pH	Yes	No
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.

omnia EDUCATION

37

Ibrexafungerp: Phase 2b DOVE Study

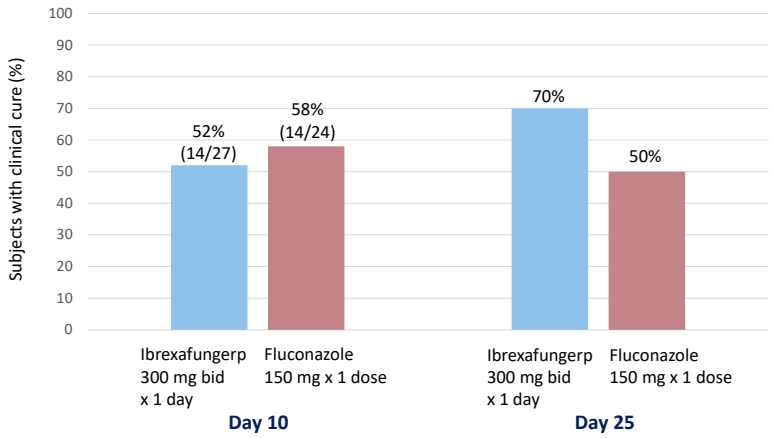
- Randomized, multicenter, double-blind, active-controlled, dose-finding study
- Evaluate the efficacy and tolerability of 5 dose levels of oral ibrexafungerp vs fluconazole
- Women with moderate to severe acute VVC
- Primary goal: clinical cure
- Randomized to:
  - Ibrexafungerp 150 mg bid x 3 days
  - Ibrexafungerp 300 mg bid x 3 days
  - Ibrexafungerp 300 mg bid x 1 day
  - Ibrexafungerp 450 mg bid x 1 day
  - Ibrexafungerp 750 mg x 1 dose
  - Fluconazole 150 mg single dose (per FDA-approved dose)

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

omnia EDUCATION

38

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



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.

omnia EDUCATION

39

The DOVE Study: Safety Outcomes

- Generally safe and well tolerated
- No serious adverse events or discontinuations
- Higher incidence of mild to moderate GI events of short duration
  - Nausea
  - Diarrhea
  - Abdominal pain
- No drug-related serious adverse events in any treatment arm

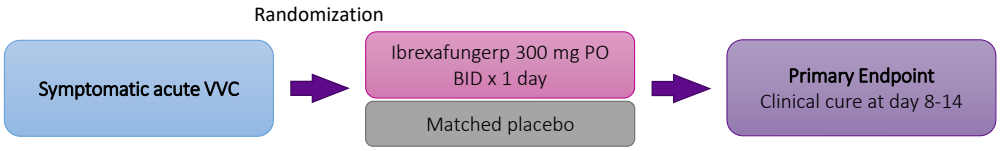
Cadet R, et al. *Obstet Gynecol*. 2019;133:113S-114S.

omnia EDUCATION

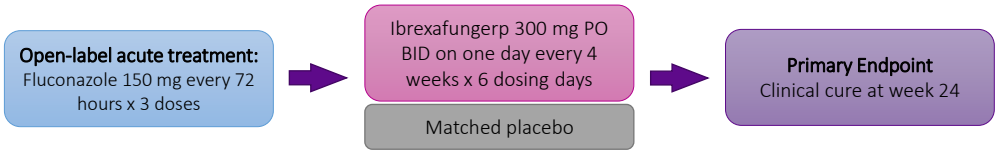
40

Ibrexafungerp: Ongoing Phase 3 Trials for Acute VVC and RVVC

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



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

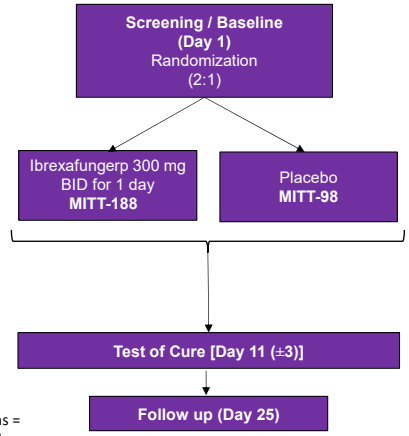


omnia EDUCATION

41

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.

omnia EDUCATION

42

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

omnia EDUCATION

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

VANISH-303: Demographics and Baseline Characteristics

MITT	VANISH-303	
	Ibrexafungerp 300mg 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)

omnia EDUCATION

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

VANISH-303: Efficacy Endpoints

MITT	Ibrexafungerp 300mg 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**
****SAE's underlined**

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

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

Advantages of Investigational Agents Over Fluconazole

Oteseconazole and Ibrexafungerp 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

omnia EDUCATION