CANDLE: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Once Monthly Oral Ibrexafungerp for Prevention of Recurrent Vulvovaginal Candidiasis (VVC)

Shelagh Larson, DNP, APRN, WHNP-bc, NCMP

NPWH NURSE PRACTITIONERS IN WOMEN'S HEALTH *Caring for Women*

BACKGROUND

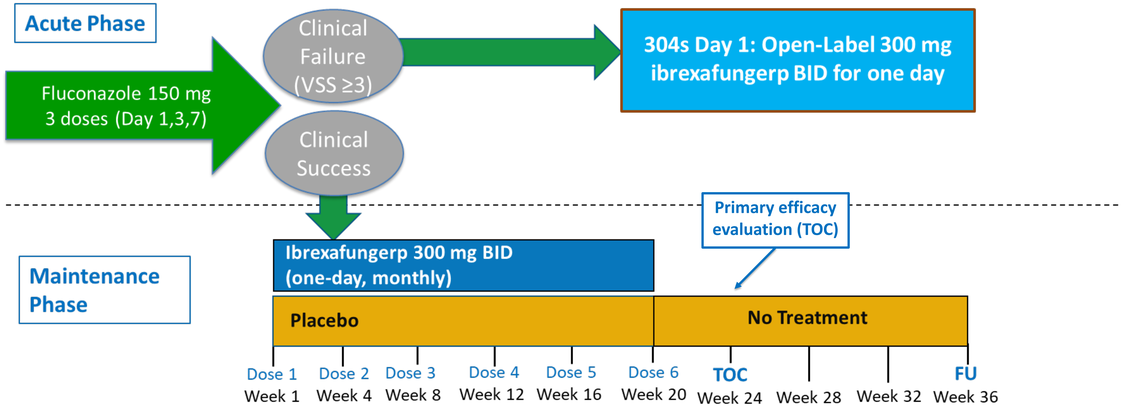
- Apprximately 75% of all women are affected by *at least* one episode of vulvovaginal candidiasis (VVC) during their lifetime
- 10 million office visits per year for vaginal symptoms
- Recurrent candidiasis is a significant clinical problem
  - Recurrent is defined by CDC (2021 guideline update) as ≥3 cases per 12 successive months
  - Approximate 5-8% globally suffer from recurrent VVC
- Azoles are indicated for VVC, and fluconazole is standard therapy
  - Resistance is a problem
  - Lack of efficacy against non-*albicans Candida*
- Ibrexafungerp is an oral triterpenoid antifungal that was approved in 2021 for the treatment of acute VVC.
- Ibrexafungerp offers several positive treatment attributes:
  - Broad-spectrum coverage against *Candida* spp., including non-*albicans Candida*
  - Over 2,000 patients have been exposed with no safety signals (contraindicated in pregnancy based on preclinical data)
  - Oral formulation in a single-day treatment
  - Activity against fluconazole-resistant strains, potency not affected by vaginal pH (~4.5)
  - High vaginal tissue penetration (9X plasma levels in animal models)
- **To provide evidence of the efficacy of ibrexafungerp in prevention of recurrent VVC, the CANDLE Study was undertaken.**

CANDLE DESIGN

Acute VVC Phase: treating active infection in a recurrent VVC subject
Subjects with diagnosis of symptomatic VVC at baseline
- Receives 3 doses of fluconazole (Days 1, 3, 7)
- Clears VVC infections move to maintenance phase [If no clearance, subjects have option of entering into sub-study with a one-day dose of ibrexafungerp (304S)]

MAINTENANCE VVC Phase: prevention of RVVC during 6 months of treatment
Subjects that have resolved their symptomatic VVC episode
- Receives monthly ibrexafungerp for 6 doses or placebo

CANDLE STUDY DESIGN



RECURRENCE DEFINITIONS

	Requiring Antifungal	VSS >3	Culture Positive	KOH microscopy
Mycologically Proven Recurrence	X	X	X	Positive or negative
Presumed Recurrence	X	X		X
Suspected Recurrence	X			

- **Mycologically Proven Recurrence:** An episode of VVC with a **total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp.** that required antifungal treatment.
- **Presumed Recurrence:** An episode of VVC with a **total composite score ≥ 3 on the VSS Scale** that required antifungal treatment and for which there is a **positive KOH microscopy but no positive fungal culture.**
- **Suspected Recurrence**: An episode of VVC that **required treatment with an antifungal agent** (including self-administration with over-the-counter antifungals) **regardless of VSS composite score but for which there is no mycological evidence of disease, such as a positive KOH microscopy or fungal culture**.

BASELINE CHARACTERISTICS

ITT population	Ibrexafungerp (N= 130)	Placebo (N= 130)
Age, Median (Min, Max)	33 (18, 65)	33 (18, 61)
Race % White | % African American	92% | 7%	88% | 9%
Body Mass Index (kg/m²) Median (Min, Max)	23.7 (18, 48)	23 (17, 49)
Percent BMI >= 30	20.7%	12.3%
***Candida* species (screening culture), %**		
Candida albicans	93.8%	93.8%
Candida glabrata	4.7%	3.8%
Composite Vulvovaginal Signs and Symptoms Score at Screening, Median (Min, Max)	10 (4, 17)	10 (4, 17)

RESULTS

Table 1. Efficacy Endpoints Endpoint ITT population	Ibrexafungerp (N= 130) n (%)	Placebo (N= 130) n (%)	Relative Risk (95 % CI) P value
Clinical Success (no recurrence: mycologically proven, presumed, or suspected VVC) at TOC (Week 24) (primary)	85 (65.4)	69 (53.1)	1.24 (1.034, 1.486) **P=0.020**
No Mycologically Proven Recurrence at TOC (week 24) (key secondary)	92 (70.8)	76 (58.5)	1.22 (1.032, 1.430) **P=0.019**
Clinical Success at Follow Up (Week 36)	75 (57.7)	60 (46.2)	1.26 (1.017, 1.555) **P=0.034**
No Mycologically Proven Recurrence at Follow Up (Week 36)	85 (65.4)	70 (53.8)	1.22 (1.021, 1.456) **P=0.029**

Table 2. Number of Recurrences	Ibrexafungerp (n=130)	Placebo (n=130)
At Test of Cure (Week 24)		
0 episodes	85 (65.4%)	69 (53.1%)
1 episode	27 (20.8%)	27 (20.8%)
2-3 episodes	15 (11.5%)	25 (19.2%)
≥4 episodes	3 (2.3%)	9 (6.9%)
At Follow-Up (Week 36)		
0 episodes	75 (57.7%)	60 (46.2%)
1 episode	36 (27.7%)	33 (25.4%)
2-3 episodes	12 (9.2%)	23 (17.7%)
≥4 episodes	7 (5.4%)	14 (10.8%)

Table 3. Adverse Events n=patients (%)	Ibrexafungerp N=130	Placebo N=130
Abdominal pain[1]	13 (10.0)	9 (6.9)
Diarrhea	10 (7.7)	5 (3.8)
Headache[2]	8 (6.2)	1 (0.8)
Nausea	7 (5.4)	5 (3.8)
Urinary tract infection	5 (3.8)	1(0.8)
Fatigue	4 (3.1)	0

- **Table 1. Primary and key secondary endpoints met:** Efficacy demonstrated by Clinical Success (defined as subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected Recurrences of VVC) up to TOC (Week 24).
- Efficacy demonstrated with no Mycologically Proven Recurrence (defined as an episode of VVC with a total composite score ≥3 on the Vulvovaginal Signs and Symptoms [VSS] Scale and a culture positive for *Candida* spp. that required antifungal treatment) at TOC (Week 24).
- **Table 2. Ibrexafungerp reduced the recurrence of VVC** in patients at Week 24 and at Week 36 (p<0.002 at Week 24, p<0.004 at Week 36)
- **Table 3. Adverse event profile is consistent** with previous studies of ibrexafungerp in treatment of acute VVC.

CONCLUSIONS

Ibrexafungerp demonstrated efficacy and was well-tolerated for the prevention of recurrent vulvovaginal candidiasis in this population of women aged 18 to 65 years.

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