Appendix 1

Secnidazole Treatment of Bacterial Vaginosis: Phase 2 Randomized, Blinded, Placebo-controlled Study

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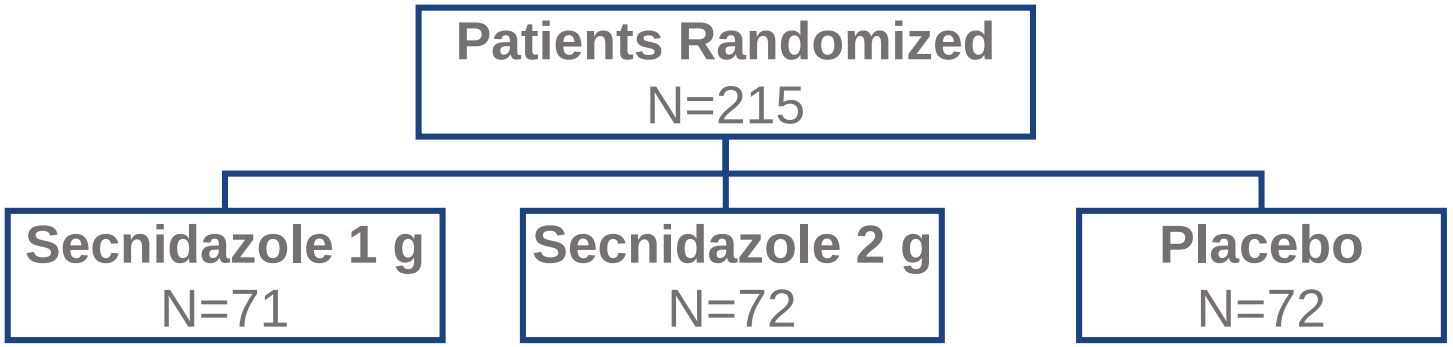
Background

- A novel oral granule formulation of secnidazole, a 5-nitroimidazole, is under development in the US
  - *Single dose* treatment option for bacterial vaginosis (BV)
- Secnidazole has a longer half-life (~17 hr) than metronidazole (~8 hr)

Secnidazole granules

Study Design

- 215 women were randomized 1:1:1 at 24 US sites to **single oral doses** of 1 or 2 grams of secnidazole or placebo granules



- Inclusion Criteria:
  - ≥18 years of age
  - Met the 4 Amsel criteria for BV (discharge, pH ≥ 4.7, ≥20% clue cells, positive whiff test)
  - Nugent scores ≥4*

*Nugent scores were analyzed centrally and were only available to investigators after patients had been randomized and treated based on clinical assessments.

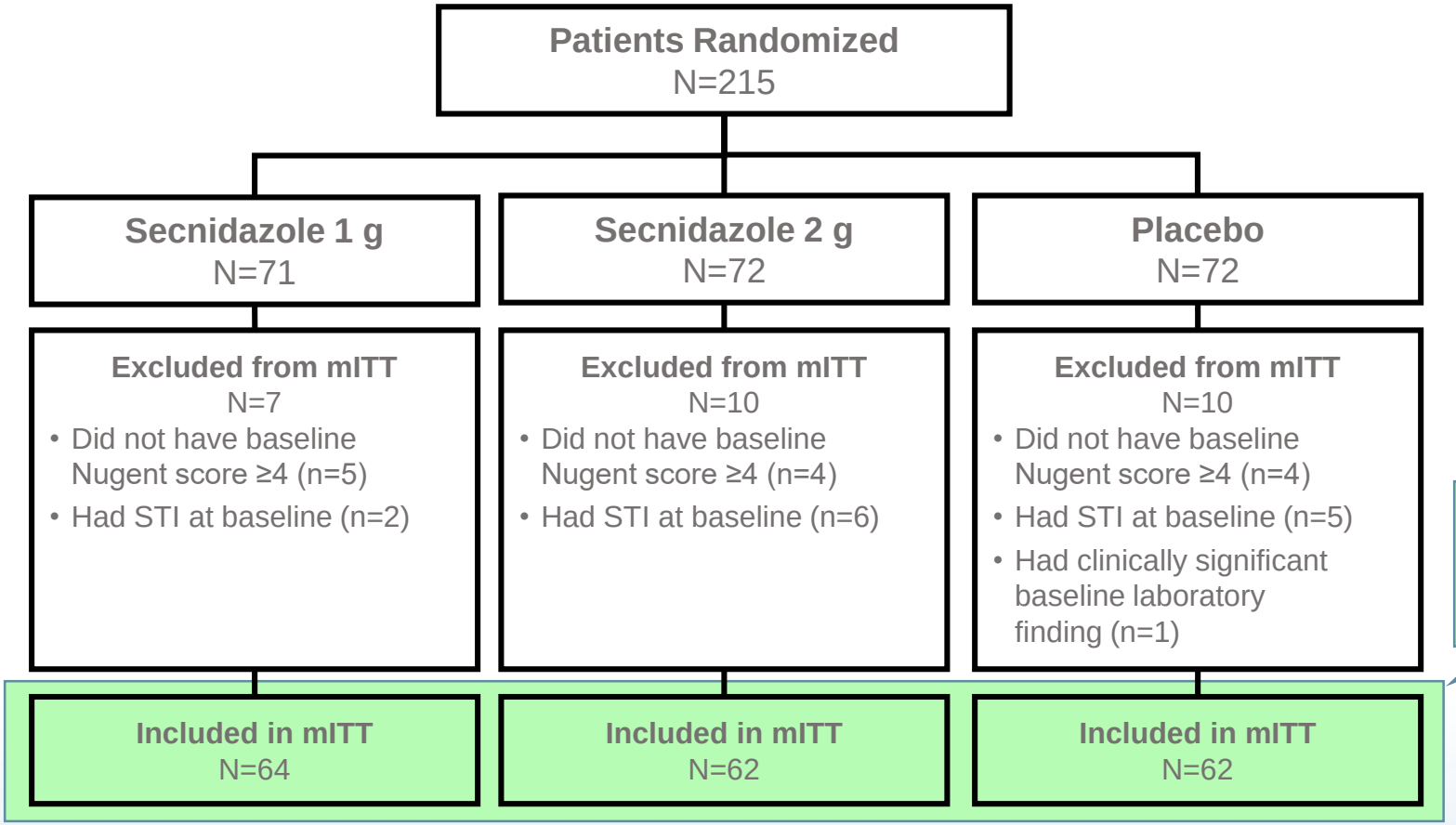
Study Outcomes

- Efficacy was evaluated at 21–30 days post treatment
- The efficacy analyses were performed on the modified Intention-to-Treat (mITT)* population, defined as all randomized patients who met all study selection criteria

Primary Endpoint	Secondary Endpoints	Safety Evaluations
• Clinical cure defined as normal discharge, negative whiff test, and clue cells <20%	• Microbiological cure: Nugent score of 0-3 • Therapeutic cure: both clinical and microbiological cure	• Assessment of treatment-emergent adverse events (AEs) • Physical examination findings • Vital signs • Clinical safety laboratory results

*All statistical comparisons used a stratified Cochran-Mantel-Haenszel (CMH) test performed at a 0.05 level of significance (2-sided).

Patient Disposition

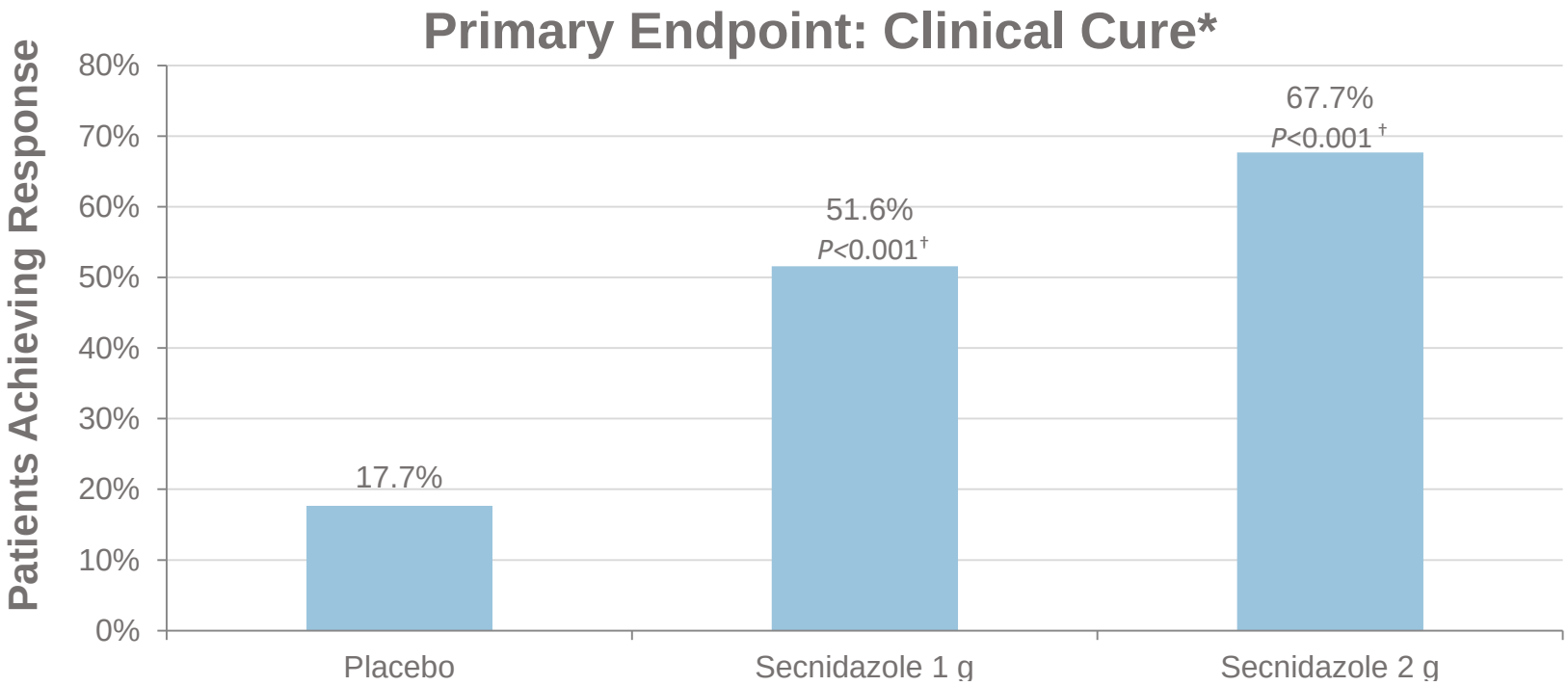


Patient Demographic and Baseline Characteristics

Overall and by Treatment Group (mITT Population)

Parameter/Statistic	Secnidazole 1 g N=64 (%)	Secnidazole 2 g N=62 (%)	Placebo N=62 (%)	Overall N=188 (%)
Age (years)				
Median (Min, Max)	34 (19, 49)	31 (19, 54)	33 (19, 49)	33 (19, 54)
Race, n (%)				
White	18 (28.1)	32 (51.6)	24 (38.7)	74 (39.4)
Black/African American	42 (65.6)	26 (41.9)	34 (54.8)	102 (54.3)
Asian	1 (1.6)	1 (1.6)	2 (3.2)	4 (2.1)
American Indian/Alaska Native	1 (1.6)	1 (1.6)	0	2 (1.1)
Other	2 (3.1)	2 (3.2)	2 (3.2)	6 (3.2)
Number of BV episodes in past 12 months				
Median (Min, Max)	3 (1, 13)	2 (1, 12)	3 (1, 12)	3 (1, 13)
BV strata: number of BV episodes in past 12 months, n (%)				
≤3	44 (68.8)	41 (66.1)	43 (69.4)	128 (68.1)
≥4	20 (31.3)	21 (33.9)	19 (30.6)	60 (31.9)
Baseline Nugent Score				
Median (Min, Max)	9 (5, 10)	8 (4, 10)	8 (4, 10)	8 (4, 10)

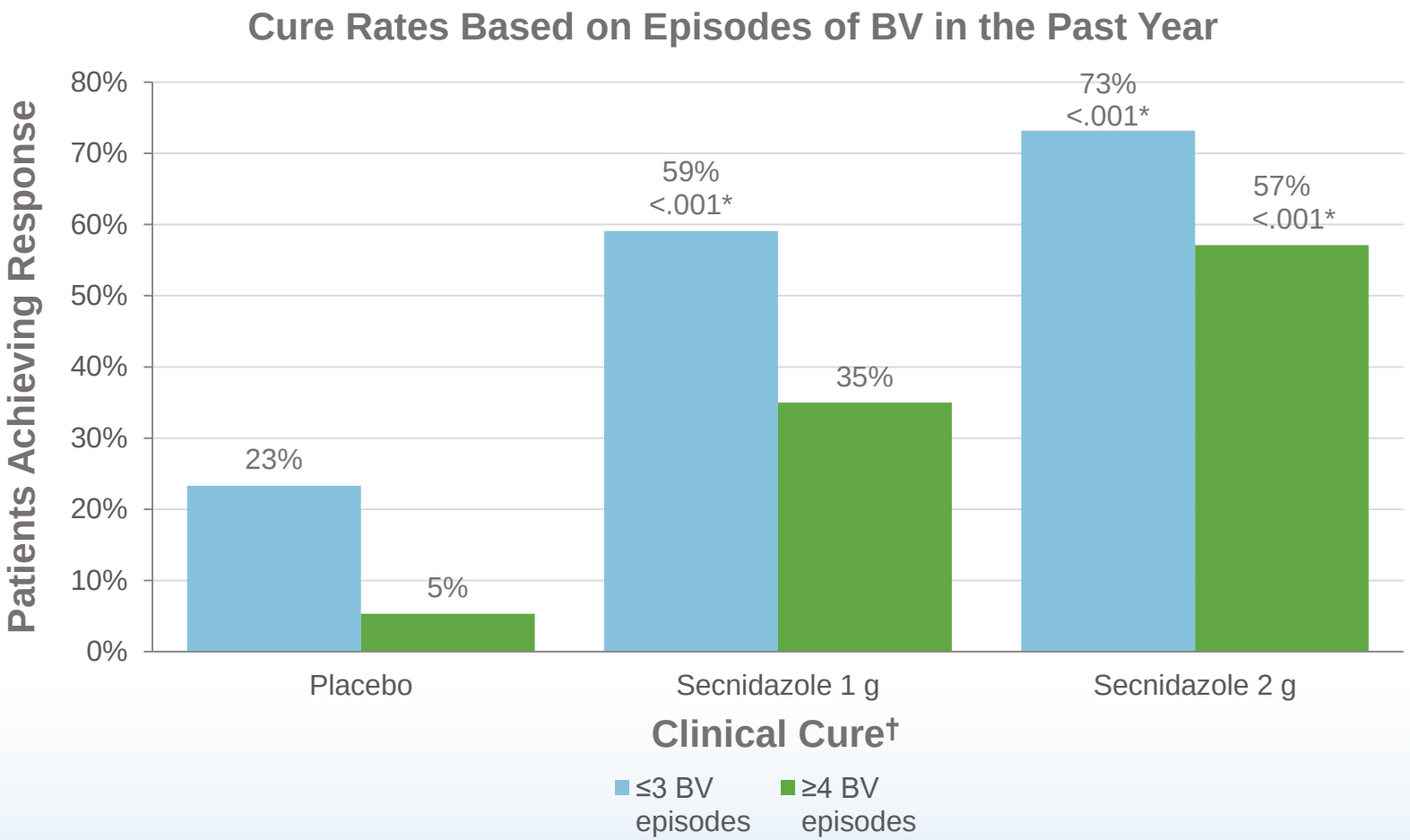
Efficacy Outcomes for Clinical Cure (mITT Population)



- In the ITT population, the clinical cure rate was 49.3% for the 1 g group, 65.3% for the 2 g group, and 19.4% for the placebo group
- The mITT population, shown here, was prespecified as the primary analysis population

*Clinical cure was defined as a patient who had all 3 of the following at days 21–30: normal vaginal discharge, negative KOH whiff test, and clue cells <20%. †*P* value vs placebo from a Cochran-Mantel-Haenszel test adjusted for bacterial vaginosis strata.

Clinical Cure Rates Stratified by Number of Episodes of BV in the Past Year



**P* value vs placebo from a CMH test adjusted for BV strata (≤3 or ≥4 episodes in the past 12 months). †Clinical cure was defined as a patient who had normal vaginal discharge, negative KOH whiff test, and clue cells <20% at days 21–30

Patient Incidence of Treatment-emergent Adverse Events (N=215)*

Treatment-Emergent Adverse Event (TEAE)

	Secnidazole 1 g (N=71)	Secnidazole 2 g (N=72)	Placebo (N=72)
Total number (%) of participants reporting ≥1 TEAE, n (%)	9 (12.7)	14 (19.4)	7 (9.7)
Any TEAEs with Incidence ≥2% Infections, n (%)			
Yeast infections†	3 (4.2)	2 (2.8)	2 (2.8)
Upper respiratory tract infection	0 (0)	0 (0)	2 (2.8)
Treatment-related‡ TEAEs ≥1%			
Yeast infection	0 (0)	2 (2.8)	1 (1.4)
Vulvovaginal pruritus	0 (0)	1 (1.4)	0 (0)
Chromaturia	0 (0)	1 (1.4)	0 (0)
Dysgeusia	0 (0)	1 (1.4)	0 (0)
Headache	1 (1.4)	0 (0)	0 (0)
Nausea	0 (0)	1 (1.4)	0 (0)
Alanine aminotransferase increased	0 (0)	1 (1.4)	0 (0)
Aspartate aminotransferase increased	0 (0)	1 (1.4)	0 (0)

*Safety population consisted of all randomized patients who received study drug. †Investigators reported yeast infections using any of the following acceptable terms: vulvovaginal mycotic infection, Candida infection, Fungal infection, or vulvovaginal candidiasis
‡Adverse events that were deemed by the investigator to be “possibly” or “probably” related to treatment. All treatment-related TEAEs were considered mild to moderate.

Study Conclusions

- This study was part of the clinical development program for a novel oral granule formulation of secnidazole
  - Diagnosis and cure were defined based on draft FDA guidance for the treatment of BV
- Both the 1 and 2 g doses of secnidazole granules were more effective compared to placebo
- Greater efficacy was observed consistently with the 2 g dose, even among women having four or more episodes of BV in the previous year
- All treatment emergent AEs were mild or moderate in intensity, with no serious adverse events reported

Funding and Conflict of Interest

- Funding for this study was provided to Magee-Womens Research Institute (Hillier), Drexel University (Nyirjesy), Downtown Women's Health Care (Waldbaum), the University of Alabama (Schwebke), and Tidewater Clinical Research, Inc. (Morgan), by Symbiomix Therapeutics, LLC, Baltimore, MD

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