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)
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

  ![Study Design Diagram]

  Patients Randomized  
  N=215

  - Secnidazole 1 g  
    N=71
  - Secnidazole 2 g  
    N=72
  - Placebo  
    N=72

• 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

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
<th>Safety Evaluations</th>
</tr>
</thead>
</table>
| - 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

Patients Randomized
N=215

Secnidazole 1 g
N=71
- Excluded from mITT
  N=7
  • Did not have baseline Nugent score ≥4 (n=5)
  • Had STI at baseline (n=2)
- Included in mITT
  N=64

Secnidazole 2 g
N=72
- Excluded from mITT
  N=10
  • Did not have baseline Nugent score ≥4 (n=4)
  • Had STI at baseline (n=6)
- Included in mITT
  N=62

Placebo
N=72
- Excluded from mITT
  N=10
  • Did not have baseline Nugent score ≥4 (n=4)
  • Had STI at baseline (n=5)
  • Had clinically significant baseline laboratory finding (n=1)
- Included in mITT
  N=62

188 women included in the efficacy analysis
### Patient Demographic and Baseline Characteristics

#### Overall and by Treatment Group (mITT Population)

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

Cure Rates Based on Episodes of BV in the Past Year

Patients Achieving Response

- Placebo: 23% cure rate
- Secnidazole 1 g: 59% cure rate, \(<.001\)
- Secnidazole 2 g: 73% cure rate, \(<.001\)

Clinical Cure†

- ≤3 BV episodes: 5% response rate
- ≥4 BV episodes: 35% response rate

*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)

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

*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