Bleeding Patterns and Endometrial Safety with a 1-Year, Segesterone Acetate*/Ethinyl Estradiol Contraceptive Vaginal System

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*Formerly known as Nestorone®
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|                 | • Research support: Estetra, EvoFem, FHI (MonaLisa), Sebela, and Mithra  
|                 | • Speaker’s bureau: Bayer Healthcare, Cooper Surgical and Merck |
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|                 | • Consultant: Danco, Estetra, Exeltis, and Medicines360  
|                 | • Research support: Dare Bioscience, Fidelity Charitable, HRA Pharma, Medicines360, Sebela, NIH/NICHD and the Society of Family Planning |
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|                 | • Research support: AbbVie, Bayer Healthcare, Dare Bioscience, Estetra SPRL, Medicines360, Merck, NIH, and NICHD |
| Dr. Mirkin      | • Employer: TherapeuticsMD with stock/stock options |
| Dr. Merkatz     | • Employer: Population Council, a not-for-profit research organization |
SA/EE 1-Year Contraceptive Vaginal System (CVS)

- A novel 1-year, ring-shaped CVS combining segesterone acetate (SA) and ethinyl estradiol (EE)
  - Reusable for 13 cycles (one year) on a 21-day in/7-day out regimen
  - Does not require refrigeration before first use or during cyclical periods of nonuse
- Approved by the FDA as Anovera™ in August 2018
  - Licensed to TherapeuticsMD, Boca Raton, FL

Delivers SA 0.15 mg/EE 0.013 mg per day 13 cycles: 3 weeks on/1 week off

8.4 mm (3/8") in cross section
58 mm (2 1/4") in diameter
Objectives

• To analyze the bleeding patterns and endometrial safety of the CVS (SA 0.15 mg/ EE 0.013 mg) for up to 13 cycles of use
Phase 3 Trials: Study Design

- Two multicenter, single-arm, open-label, pivotal, phase 3 studies evaluated the efficacy and safety of a single SA/EE CVS used on a 21-day in/7-day out regimen for up to 13 cycles
  - 300A (CCN006) study at 15 US study sites, supported by NICHD
  - 300B study at 12 international study sites, supported by USAID & WHO
    - Brazil, Chile, Dominican Republic, Finland, Hungary, Sweden, Australia, and US (5 sites)
- Basic entry requirements
  - Healthy
  - Sexually active
  - 18–40 years

Bleeding Data

• All phase 3 participants recorded in paper diaries the occurrence of vaginal bleeding and spotting daily for each 28-day cycle.

• Bleeding data by 28-day cycles were summarized for:
  • Scheduled (occurring on cycle days 22–28)
  • Unscheduled (occurring on cycle days 1 to 21)

• Factors associated with unscheduled bleeding/spotting (B/S) from the first 4 cycles of CVS use were identified using Pearson’s $\chi^2$ test and evaluated with multiple logistic regression analyses.
  • The first 4 cycles were used for this analysis
    • To avoid bias due to the varied length of time women participated in the trial
    • Early bleeding patterns can influence contraceptive discontinuation

Endometrial Safety Substudy

• Women consented to join an endometrial safety substudy at five 300A study sites\(^1\)
  • All had to have normal baseline endometrial biopsies
  • First 25 women reaching cycle 6 had repeat biopsies
  • Remaining had biopsies at cycles 12–13 or at early termination

• Biopsies evaluated by three blinded pathologists
  • If diagnoses by pathologists differed, the most severe diagnosis was used
  • Histologic changes were evaluated in women with both screening and follow-up biopsies

Disposition and Demographics (300A & 300B)

- Mean age: 26.7 ± 5.1 years
  - Most (70%) were 20 to 29 years
- Mean BMI: 24 ± 3.6 kg/m²
Bleeding Profile

• 98% of women had scheduled B/S (during ring removal days) with a mean 4.9 days per cycle\(^1\)

• 5%–10% of women per cycle reported unscheduled bleeding\(^2\)
  • Mean number of unscheduled B/S days was ≤1 day per cycle

• 3%–5% of women had complete amenorrhea per cycle\(^1\)

• Early discontinuation due to unacceptable bleeding was 1.7%\(^2\)

B/S: bleeding or spotting; IQR: interquartile range.
Demographic Factors Associated with Bleeding

- Ethnicity and race were significantly associated with unscheduled B/S
  - Black/African-American (vs White) women were more likely to report unscheduled B/S (OR 1.49; 95% CI, 1.14–1.94)
- Age, BMI, education and current smoking did not influence bleeding patterns

<table>
<thead>
<tr>
<th>Risk Factors, n (%)</th>
<th>Unscheduled B/S</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No episodes n=902</td>
<td>1–3 episodes n=833</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>278 (30.8)</td>
<td>244 (29.3)</td>
</tr>
<tr>
<td>Not Hispanic</td>
<td>624 (69.2)</td>
<td>589 (70.7)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>101 (11.2)</td>
<td>116 (13.9)</td>
</tr>
<tr>
<td>White</td>
<td>672 (74.5)</td>
<td>601 (72.1)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>129 (14.3)</td>
<td>116 (13.9)</td>
</tr>
</tbody>
</table>

*P-value by Pearson Chi-Square. BMI: body mass index; B/S: bleeding or spotting; CI: confidence interval; OR: odds ratio. B/S episode = bleeding/spotting days bound on either end by 2 days of no bleeding or spotting.

Endometrial Histology

- Of the 156 women in the endometrial safety substudy, 83 had follow-up biopsies. No cases of endometrial hyperplasia or carcinoma were identified at cycle 6 (n=24), cycles 12/13 (n=30) or at other end of therapy times (n=29).
- The most frequent histologic diagnoses were atrophic/inactive or secretory.

<table>
<thead>
<tr>
<th>Results, n (%)</th>
<th>Histologic Diagnoses</th>
<th>Baseline (n=83)</th>
<th>Cycle 6 (n=24)</th>
<th>Cycles 12-13 (n=30)</th>
<th>Other (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Insufficient or no tissue</td>
<td>4 (5)</td>
<td>0</td>
<td>3 (10)</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>Atrophic/inactive</td>
<td>6 (7)</td>
<td>7 (29)</td>
<td>8 (27)</td>
<td>8 (28)</td>
</tr>
<tr>
<td></td>
<td>Secretory</td>
<td>25 (30)</td>
<td>7 (29)</td>
<td>11 (37)</td>
<td>13 (45)</td>
</tr>
<tr>
<td></td>
<td>Proliferative</td>
<td>33 (40)</td>
<td>4 (17)</td>
<td>2 (7)</td>
<td>6 (21)</td>
</tr>
<tr>
<td></td>
<td>Menstrual</td>
<td>2 (2)</td>
<td>1 (4)</td>
<td>2 (7)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>9 (11)</td>
<td>4 (17)</td>
<td>3 (10)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Hyperplasia</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>Endometritis/polyp</td>
<td>3 (4)</td>
<td>1 (4)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

*aAll subjects with both a baseline (Screening, Visit 0) and follow-up biopsy.
*bOne woman with endometrial hyperplasia was allowed to continue participating in the study.

Conclusions

• Participants using the SA/EE CVS for up to 13 cycles experienced cycle control with a planned withdrawal bleed every 28 days\textsuperscript{1}
  • Mean number of unscheduled B/S days was ≤1 day per cycle\textsuperscript{2}
• Discontinuation rate due to unacceptable bleeding (1.7%) was very low\textsuperscript{2}
• Endometrial histology confirmed endometrial safety\textsuperscript{3}
• SA/EE CVS (Annovera\textsuperscript{TM}) is an effective,\textsuperscript{4} convenient, easily-used,\textsuperscript{5} new contraceptive method with an acceptable safety profile\textsuperscript{3}

THANK YOU

To the 3000+ women volunteers from 4 continents who helped us develop Annovera

The Investigators, sub investigators, coordinators and other dedicated staff at clinical sites

Product development scientists, statistical, data management, regulatory, legal and support staff

Donors!