Segesterone Acetate/Ethinyl Estradiol 1-Year Contraceptive Vaginal System Safety Evaluation

Michael A Thomas, MD; Kristina Gemzell-Danielsson, MD; Mitchell D Creinin, MD; Kurt T Barnhart, MD; Maria José Miranda, MD; Regina Strik-Ware, MD

1.University of Cincinnati; Cincinnati, OH, USA; 2.Karolinska University Hospital, Stockholm, Sweden; 3.University of California, Davis, Sacramento, CA, USA; 4.University of Pennsylvania; Philadelphia, PA, USA; 5.Instituto Chileno de Medicina Reproductiva (ICMER); Santiago, Chile; 6.Population Council; New York, NY, USA

Introduction

• Segesterone acetate (SA) 150 mg/day and ethinyl estradiol (EE) 13 mg/day contraceptive vaginal system (CVS)1
• Annovera™ (TherapeuticsMD), US approval August 2018
• Self-inserted and used in 21/7 day cycle for up to 13 cycles (1 year)
• Does not require refrigeration
• SA is non-craey active2
• Inhibits ovulation at very low dose
• Blinds with high specificity to progestosterone receptor
• No binding or transactivation of androgen receptors

Objective

To evaluate clinical safety outcomes from nine studies, including the impact of microbiology, and liver proteins from 3 US-based phase 3 substudy sites

Methods

Pooled data from four studies conducted with the final manufactured CVS

• One-year pharmacokinetic study conducted at 3 study sites in the US (1) and Latin America (2)
• Two identical, 1-year, phase-3, single arm, open-label multinational studies with sites in the US (20), Europe (3), Latin America (3) and Australia (1) with a 1-year extension from one of these studies
• Safety population included all women who inserted the CVS
• Safety evaluated by AE reporting, and endometrial biopsies, vaginal microbiology, and liver proteins from 3 US-based phase 3 substudy sites
• Data safety monitoring board (DSMB) recommended discontinuation and cessation of enrolment of women with BMI >29 kg/m2 after 2 women with BMI >29 kg/m2 had a VTE during first 6 cycles of use

Results

• Combined study population: 3052 women
• 2308 (76.5%) received final manufactured CVS; 999 (43.3%) completed
• 209 women with BMI >29 kg/m2 were enrolled; 36/209 (17%) completed

• Expulsions occurred most frequently during the initial cycle of use
• No clinically relevant or significant mean changes in total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, or glucose
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• No clinically relevant changes in liver enzymes, lipid profile, body mass index, and other standard laboratory tests

Safety

Adverse events

• 1602 (69%) women experienced treatment-related TEAEs (Figure 2)
• 1602 (69%) women experienced treatment-related TEAEs (Table 1)
• 2308 (75.6%) received final manufactured CVS; 999 (43.3%) completed
• 209 women with BMI >29 kg/m2 were enrolled; 36/209 (17%) completed

• Expulsions occurred most frequently during the initial cycle of use

Clinical laboratory values, vital signs and physical exam

• No safety signals from standard laboratory chemistry, hematology, vital signs, or physical exams

• Expulsions occurred most frequently during the initial cycle of use

Table 1. Phase 3 treatment-emergent AE overall and by BMI subgroup

<table>
<thead>
<tr>
<th>BMI category</th>
<th>Total</th>
<th>% Man</th>
<th>% Woman</th>
<th>n (BMI 20-29)</th>
<th>% Man</th>
<th>% Woman</th>
<th>n (BMI ≥30)</th>
<th>% Man</th>
<th>% Woman</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2308</td>
<td>237</td>
<td>957</td>
<td>1392</td>
<td>294</td>
<td>916</td>
<td>946</td>
<td>53</td>
<td>47</td>
</tr>
<tr>
<td>BMI 20-29</td>
<td>1392</td>
<td></td>
<td>957</td>
<td>415</td>
<td></td>
<td>916</td>
<td>564</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>916</td>
<td></td>
<td>415</td>
<td>270</td>
<td></td>
<td>564</td>
<td>382</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Venous thromboembolic events by cycle and any risk factor

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Low risk (%)</th>
<th>Medium risk (%)</th>
<th>High risk (%)</th>
<th>Venous thromboembolic events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>281 (12)</td>
<td>572 (25)</td>
<td>355 (15)</td>
<td>16 (0.7)</td>
</tr>
<tr>
<td>20</td>
<td>1332 (57)</td>
<td>2357 (57)</td>
<td>999 (43)</td>
<td>20 (0.8)</td>
</tr>
<tr>
<td>40</td>
<td>1706 (69)</td>
<td>2924 (66)</td>
<td>1293 (54)</td>
<td>20 (0.8)</td>
</tr>
<tr>
<td>60</td>
<td>2099 (90)</td>
<td>3561 (90)</td>
<td>1790 (78)</td>
<td>20 (0.8)</td>
</tr>
<tr>
<td>80</td>
<td>2492 (100)</td>
<td>4295 (100)</td>
<td>2292 (95)</td>
<td>20 (0.8)</td>
</tr>
</tbody>
</table>

Table 3. Mean changes from baseline to end of study in lipids and glucose

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Mean change from baseline (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>7.5 ± 8.7</td>
</tr>
<tr>
<td>HDL</td>
<td>5.5 ± 4.3</td>
</tr>
<tr>
<td>LDL</td>
<td>4.5 ± 3.6</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.5 ± 1.5</td>
</tr>
<tr>
<td>Glucose</td>
<td>6.6 ± 1.5</td>
</tr>
</tbody>
</table>

Disclosures

• MAT has received research support (paid to the university of Cincinnati Medical Center) from Bayer Healthcare and Therapeutics (2009-2010), and TherapeuticsMD (2016-2018). MAT serves on advisory boards for Genentech, Inc., and Boehringer Ingelheim, and has received research support from Genentech, Inc., and Boehringer Ingelheim.

References