17β-Estradiol/Progesterone in a Single Oral Softgel Capsule (TX-001HR) Significantly Reduced Moderate-to-Severe Vasomotor Symptoms without Endometrial Hyperplasia

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Objective: To evaluate the efficacy and safety of four TX-001HR (estradiol [E2] combined with progesterone [P4]) doses versus placebo for the treatment of moderate-to-severe vasomotor symptoms (VMS)

Design: Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in menopausal women with an intact uterus (NC0015426656)

Background

• Use of compounded bioidentical hormone therapy (CBHT) has become highly prevalent in the US since the 2002 WHI report1  
  • An estimated 1 to 2.5 million US women use unapproved compounded products,1 representing up to 21 to 39 million prescriptions annually2,3  
  • Some compounded products may be associated with increased risks4  
  • Reports5-7 and a NAMS survey (n=1064) suggest an increase in uterine bleeding and endometrial hyperplasia/lesions with CBHT  
  • CBHT products are not FDA-approved and NAMS/ACOG/ENDO societies6,7,8 recommend against the use of CBHT  
  • No HT formulation combining 17β-estradiol and progesterone is FDA approved  
  • TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational combination of 17β-estradiol and progesterone (sometimes referred to as bioidentical hormones) in a single, oral, softgel capsule

Disclosures

• Research support: Actavis, Bayer Healthcare, Endoceutics, Glenmark, Merck, Radius Health, Shionogi, and TherapeuticsMD

• Consultant: Abbvie, Actavis, Agile Therapeutics, Bayer Healthcare, Endoceutics, Exelis, Innovagyn, Merck, Pfizer, Radius Health, Sermonix, Shionogi, Teva Women’s Healthcare, and TherapeuticsMD

REPLENISH Trial: Objective and Design

• Objective: To evaluate the efficacy and safety of four TX-001HR (estradiol [E2] combined with progesterone [P4]) doses versus placebo for the treatment of moderate-to-severe vasomotor symptoms (VMS)

• Design: Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in menopausal women with an intact uterus (NC0015426656)

1 1-year endometrial safety study and 12-week efficacy substudy for the treatment of VMS
Key Inclusion Criteria

- Healthy menopausal women aged 40-65 years
- Intact uterus
- Body mass index ≤34 kg/m²
- Vasomotor symptoms associated with menopause
- Acceptable endometrial biopsy results

**VMS Substudy**
- ≥7/day or ≥50/week moderate-to-severe hot flushes

Key Exclusion Criteria

- History of hyperplasia or neoplasia of hormone dependent tissues
- History of thrombosis of deep veins/arteries
- Abnormalities of the gastrointestinal system
- Abnormal function of other hormone producing glands
- Prior use of estrogen-, progestogen-, androgen-, SERM products
- Medications known to induce or affect estrogen and/or progestogen drug metabolism or activity

**Study Design: Randomization**

- **VMS substudy**
  - ≥7/day or ≥50/week moderate-to-severe hot flushes
  - Randomized 1:1:1:1:1
- **General study**
  - Did not qualify for VMS substudy
  - Randomized 1:1:1:1
- TX-001HR was taken daily for 12 months (VMS substudy was 12 weeks)
- Both populations were assessed for general and endometrial safety
- All women completed a daily diary on the frequency and severity of their VMS through week 12

**REPLENISH Trial: Study Endpoints**

<table>
<thead>
<tr>
<th>Endpoints Description</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>4 co-primary endpoints</td>
<td>Primary</td>
</tr>
<tr>
<td>VMS frequency (moderate-to-severe)</td>
<td>Mean change from baseline to week 4</td>
<td>Incidence of endometrial hyperplasia with up to 12 months of treatment (in women with endometrial biopsies)</td>
</tr>
<tr>
<td>VMS severity</td>
<td>Mean change from baseline to week 12</td>
<td>Incidence of adverse events (AEs) and serious AEs</td>
</tr>
<tr>
<td>Secondary</td>
<td>Mean change in frequency and severity of moderate-to-severe VMS from baseline for each week up to week 12</td>
<td></td>
</tr>
</tbody>
</table>
Statistical Analyses

• Efficacy analyses were performed on the modified intent-to-treat (MITT) population of the VMS substudy

  • MITT VMS substudy included women who took ≥1 dose of study treatment, had ≥15 days of VMS diary data at baseline, and 24± days of VMS diary data for 1 on-treatment week

  • Each TX-001HR dose was compared with placebo and tested for the 4 co-primary efficacy endpoints at alpha level 0.05 (two-tailed) using a mixed model repeated measures (MMRM) analysis

• Endometrial safety was analyzed in women who took ≥1 capsule, had an acceptable biopsy at baseline, and had a biopsy at month 12 or had a diagnosis of endometrial hyperplasia prior to month 12

• AEs and serious AEs were descriptively summarized in all women who took ≥1 capsule (safety population)

Demographics of VMS Substudy

• Mean age: 55 years (range, 40 to 65) and mean BMI: 27 kg/m²

  • 67% of the women were white and 31% were black

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>0.25 mg E2/50 mg P4</th>
<th>0.5 mg E2/100 mg P4</th>
<th>0.75 mg E2/150 mg P4</th>
<th>1.0 mg E2/200 mg P4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [y]</td>
<td>76 ± 20</td>
<td>76 ± 20</td>
<td>75 ± 20</td>
<td>76 ± 20</td>
<td>76 ± 20</td>
</tr>
<tr>
<td>Race [%]</td>
<td>White</td>
<td>56.8 ± 6.8</td>
<td>56.8 ± 6.5</td>
<td>56.8 ± 6.6</td>
<td>56.8 ± 6.0</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>43.2 ± 9.0</td>
<td>43.2 ± 9.5</td>
<td>43.2 ± 9.4</td>
<td>43.2 ± 9.0</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>Mean ± SD</td>
<td>26.6 ± 3.3</td>
<td>27.3 ± 3.5</td>
<td>26.6 ± 3.3</td>
<td>26.6 ± 3.8</td>
</tr>
</tbody>
</table>

Weekly Reduction in VMS Frequency

• All TX-001HR doses provided statistically significant and clinically meaningful reductions in the weekly frequency of moderate-to-severe VMS from baseline at weeks 4 and 12 versus placebo

  • Except for 0.5 mg E2/50 mg P4, which reached significance at week 6

  • Mean daily number of moderate-to-severe VMS decreased from 10–12/day at baseline to 2–4/day with TX-001HR (5/day for placebo) at week 12

  *Other included investigator decision, lack of efficacy, protocol deviation and other

Disposition

• 89% of women completed the VMS substudy at 12 weeks

<table>
<thead>
<tr>
<th>Population [%]</th>
<th>Completed at 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1845</td>
</tr>
<tr>
<td>Total n [n]</td>
<td>141 149 147 154 135</td>
</tr>
<tr>
<td>Randomized</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>131 129 131 143 138</td>
</tr>
<tr>
<td>Randomized to treatment [n]</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>100 100 100 100 100</td>
</tr>
<tr>
<td>Screen failures</td>
<td>n=3175</td>
</tr>
<tr>
<td>n</td>
<td>147 153 142 140 139</td>
</tr>
<tr>
<td>Did not take 1 capsule [n]</td>
<td>100</td>
</tr>
<tr>
<td>n</td>
<td>131 129 131 143 138</td>
</tr>
</tbody>
</table>

Did not take 1 capsule: 100%

Subjects screened for eligibility, n=1000

Population, n=1000

Completed at 12 weeks
Weeklly Improvement in VMS Severity

- Doses 1.0 mg E2/100 mg P4 and 0.5 mg E2/100 mg P4 significantly improved the severity of VMS at weeks 4 and 12 compared with placebo
  - 0.5 mg E2/50 mg P4 was significant at weeks 7, 9–12
  - 0.25 mg E2/50 mg P4 was significant at weeks 6, 7 and 9

Endometrial Safety

- Endometrial hyperplasia incidence was 0%
- No endometrial malignancies detected with any TX-001HR dose or placebo at 12 months

<table>
<thead>
<tr>
<th>Treatment, n (%)</th>
<th>Endometrial Hyperplasia</th>
<th>0.25 mg E2/50 mg P4</th>
<th>0.5 mg E2/50 mg P4</th>
<th>1.0 mg E2/50 mg P4</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>92</td>
</tr>
<tr>
<td>Hyperplasia at 12 months: incidence rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 episodes/patient</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>3+ episodes/patient</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Proliferation endometrium*: Screening</td>
<td>3 (1.5)</td>
<td>5 (2.5)</td>
<td>5 (2.5)</td>
<td>3 (1.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Month 12</td>
<td>6 (3.0)</td>
<td>5 (2.5)</td>
<td>1 (0.5)</td>
<td>3 (1.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Endometrial polyp*: Screening</td>
<td>3 (1.5)</td>
<td>7 (3.5)</td>
<td>5 (2.5)</td>
<td>5 (2.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Month 12</td>
<td>4 (2.0)</td>
<td>6 (3.0)</td>
<td>3 (1.5)</td>
<td>7 (3.5)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

Safety Endpoints

- Incidence of TEAEs was low and most TEAEs were mild or moderate in severity
- Most frequently reported TEAEs (≥5%) were headache, nasopharyngitis, breast tenderness, upper respiratory tract infection, nausea, back pain, abdominal pain
- Serious AEs reported were low and consistent with the age and population studied
- 7 serious AEs were considered related to treatment
- Minimal clinically meaningful changes in lipid, coagulation and glucose parameters
- No unexpected safety signals were observed

TEAE: Treatment-emergent adverse event
Conclusions

Significant and clinically meaningful improvements versus placebo were observed with

- TX-001HR doses 1.0 mg E2/100 mg P4 or 0.5 mg E2/100 mg P4 in the frequency and severity of moderate-to-severe VMS at weeks 4 and 12
- TX-001HR 0.5 mg E2/50 mg P4 in the frequency of moderate-to-severe VMS by week 6 and severity at most time points from weeks 7 to 12
- TX-001HR 0.25 mg E2/50 mg P4 in the frequency, but not severity, of moderate-to-severe VMS at weeks 4 and 12

Conclusions

- This TX-001HR clinical trial provided evidence of endometrial protection
- TX-001HR, if approved, would represent a new oral HT option for menopausal women with moderate-to-severe VMS who have an intact uterus
- TX-001HR may be a new option for the estimated millions of women currently using unapproved compounded BHT, which is associated with safety concerns