Effects of TX-001HR on Uterine Bleeding Rates in Menopausal Women with Vasomotor Symptoms

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Disclosures

• **Advisory board:** Abbvie, Allergan, IBSA, Pfizer, and TherapeuticsMD
• **Consultant:** Cook ObGyn and Cooper Surgical
Uterine Bleeding with VMS Treatments

- Use of compounded bioidentical HT (CBHT) has become highly prevalent in the US since the 2002 WHI report\(^1\)
  - An estimated 1 to 2.5 million US women use unapproved compounded products,\(^1\) representing up to 21 to 39 million prescriptions annually,\(^1,2\) becoming a leading therapy in the US

- Reports\(^3-6\) and a NAMS survey (n=1064)\(^7\) suggest an increase in uterine bleeding and endometrial hyperplasia/cancer with CBHT

- Vaginal or uterine bleeding regardless of therapy employed may be a sign of abnormal pathology and will lead to additional evaluation

- Compared with progestins, progesterone may have less impact on the angiogenic/antiangiogenic balance in the endometrium\(^8\)

- No HT product combining 17\(^\beta\)-estradiol and progesterone has been approved

HT: hormone therapy; NAMS: North American Menopause Society; VMS: vasomotor symptoms

REPLENISH Trial

- **Safety endpoints:** To evaluate endometrial safety (primary) and uterine bleeding (secondary) of four daily TX-001HR (E2/P4) doses versus placebo given in the REPLENISH trial to treat moderate-to-severe vasomotor symptoms
  - 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

- **Design:** Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in menopausal women with an intact uterus (NCT01942668)
  - 1-year endometrial safety study
  - 12-week efficacy substudy for the treatment of vasomotor symptoms

Study Design: Randomization

**VMS substudy (12 wks)**
- ≥7/day or ≥50/week moderate-to-severe hot flushes
- Randomized 1:1:1:1:1

**General study (12 mos)**
- Did not qualify for VMS substudy
- Randomized 1:1:1:1

**Treatment Groups**
- 1 mg E2/100 mg P4
- 0.5 mg E2/100 mg P4
- 0.5 mg E2/50 mg P4
- 0.25 mg E2/50 mg P4
- Placebo

- Both populations were assessed for general and endometrial safety
- Endometrial bleeding profiles, including cumulative amenorrhea (no bleeding or spotting) were assessed over thirteen 28-day cycles between treatment groups
  - All women completed diaries of daily bleeding (requiring sanitary protection) and spotting (not requiring sanitary protection) up to month 12

### Disposition and Demographics

- 69% of women completed at 52 weeks
- Mean age: 55 years (40–66)
- Mean BMI: 27 kg/m$^2$
- 65% were white and 32% black

#### Subjects screened for eligibility
- n=5020

#### Screen failures
- n=3175

#### Randomized to treatment
- n=1845

#### Did not take 1 capsule
- n=10

<table>
<thead>
<tr>
<th>Population, n (%)</th>
<th>Safety</th>
<th>Endometrial Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Completed at 52 weeks</td>
<td>1 mg E2/100 mg P4</td>
</tr>
<tr>
<td></td>
<td>Discontinued</td>
<td>415</td>
</tr>
<tr>
<td></td>
<td>Adverse event</td>
<td>131 (31.6)</td>
</tr>
<tr>
<td></td>
<td>Lost to follow-up</td>
<td>46 (11.1)</td>
</tr>
<tr>
<td></td>
<td>Subject withdrawal</td>
<td>27 (6.5)</td>
</tr>
<tr>
<td></td>
<td>Other*</td>
<td>36 (8.7)</td>
</tr>
<tr>
<td></td>
<td>22 (5.3)</td>
<td>14 (3.3)</td>
</tr>
</tbody>
</table>

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

Cumulative Amenorrhea

- Cumulative amenorrhea from cycle 1 to 13 was high with TX-001HR (56–73%), but lower than with placebo (81%), and increased over time
  - >90% had amenorrhea during cycle 13

Cycles are 28 days in length


*P<0.05; †P<0.01; ‡P<0.001 vs placebo.
Cumulative No Bleeding

• Women with no bleeding was high (74–90%) with TX-001HR

*P<0.05; †P≤0.01; ‡P<0.001 vs placebo.

Cycles are 28 days in length
Amenorrhea per Quarter

• Percentages of women with amenorrhea
  • 70–80% with TX-001HR vs 89% with placebo during quarter 1
  • Increased to 83–93% with TX-001HR vs 95% with placebo during quarter 4

*P<0.05; †P<0.01; ‡P<0.001 vs placebo.
Endometrial Safety

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

<table>
<thead>
<tr>
<th>Treatment, n (%)</th>
<th>Estradiol/Progesterone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg/100 mg</td>
<td>0.5 mg/100 mg</td>
</tr>
<tr>
<td>n</td>
<td>280</td>
<td>303</td>
</tr>
<tr>
<td>Hyperplasia at 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1-sided upper 95% CI</td>
<td>1.06%</td>
<td>0.98%</td>
</tr>
<tr>
<td>Proliferative endometrium*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td>2 (0.7)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Month 12</td>
<td>8 (2.9)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Endometrial polyps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td>5 (1.8)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Month 12</td>
<td>4 (1.4)</td>
<td>6 (2.0)</td>
</tr>
</tbody>
</table>

*Includes proliferative endometrium and disordered proliferative endometrium.

Adverse Events Related to Bleeding

- Few bleeding adverse events were reported*
  - TX-001HR: 1.0–4.6%
  - Placebo: 0.7%
- Discontinuation due to bleeding was low
  - TX-001HR: 0.5–1.4%
  - Placebo: 0%

*Including postmenopausal hemorrhage, uterine hemorrhage, or vaginal hemorrhage.
## Cumulative Amenorrhea Rates with HT

Based upon prescribing information or clinical data; not head-to-head comparison

<table>
<thead>
<tr>
<th>Products</th>
<th>Doses</th>
<th>Cumulative Amenorrhea (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1 to Cycle 13</td>
<td></td>
</tr>
<tr>
<td>Prempro® (CEE/MPA)¹</td>
<td>0.625 mg / 5 mg</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>0.625 mg / 2.5 mg</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>0.45 mg / 1.5 mg</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>0.3 mg / 1.5 mg</td>
<td>45</td>
</tr>
<tr>
<td>Activella® (E2/NETA)²</td>
<td>1 mg / 0.5 mg</td>
<td>49</td>
</tr>
<tr>
<td>Angeliq® (E2/DRSP)³</td>
<td>1 mg / 0.5 mg</td>
<td>45</td>
</tr>
<tr>
<td>TX-001HR (E2/P4)⁴</td>
<td>1 mg / 100 mg</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>0.5 mg / 100 mg</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>0.5 mg / 50 mg</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>0.25 mg / 50 mg</td>
<td>73</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>81</td>
</tr>
</tbody>
</table>

CEE: conjugated equine estrogens; DRSP: drospirenone; MPA: medroxyprogesterone acetate; NETA: norethisterone acetate.

Conclusions

• Amenorrhea rates were high in users of TX-001HR
  • Higher rates with TX-001HR doses than other approved hormone therapy products*

• This clinical trial provided evidence of endometrial safety with TX-001HR at 12 months
  • Absence of endometrial hyperplasia and cancer here should be considered in light of case reports of endometrial hyperplasia and cancer observed with compounded bioidentical HT use†1-4
  • Endometrial safety observed with TX-001HR highlights the need for compounded bioidentical HT safety studies given their potential risks

• If approved, TX-001HR may be an appropriate alternative combination HT with E2/P4 for treating moderate-to-severe VMS
  • Especially in the estimated millions of menopausal women currently using less regulated and unapproved compounded bioidentical HT

*Not evaluated in head-to-head comparison studies.
†Compounded bioidentical HT use ranged from unknown to several years; most were ~2 years.