Effects of Single-Capsule 17β-Estradiol/Progesterone (TX-001HR) on Metabolic Parameters and Cardiovascular Outcomes in Menopausal Women of the REPLENISH Trial

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Disclosures

• **Consultant**: Multiple pharmaceutical companies including but not limited to TherapeuticsMD
• **Stock options**: TherapeuticsMD
Background

• Menopausal vasomotor symptoms (VMS) can be effectively treated with hormone therapy (HT), which reduces hot flush frequency and severity\(^1\)

• However, HT can be associated with an increased risk of adverse events, such as venous thromboembolism (VTE), cardiovascular disease, and cerebrovascular disease\(^2-4\)

• Evidence suggests that progesterone use in HT may not negatively affect VTE risk or cardiovascular outcomes, as with synthetic progestins\(^5-7\)

• TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational combination of 17β-estradiol and progesterone in a single, oral, softgel capsule\(^8\)

REPLENISH Trial

- Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in menopausal women with an intact uterus (NCT01942668)
  - 1-year endometrial and general safety study
  - 12-week efficacy substudy for the treatment of VMS
- Additional safety endpoints
  - Metabolic parameters
  - Cardiovascular outcomes

Study Design: Randomization

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

**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

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

- TX-001HR was taken daily for up to 12 months (VMS substudy was 12 weeks)
- All participants were assessed for general and endometrial safety
- All women completed a daily diary on the frequency and severity of their VMS through week 12

Disposition and Demographics

- 69% completed at 52 weeks
- Mean age of 55 years (40–66)
- Mean BMI of 27 kg/m²
- 65% were white, 32% African American

Population, n (%)

<table>
<thead>
<tr>
<th>Safety</th>
<th>1 mg E2/100 mg P4</th>
<th>0.5 mg E2/100 mg P4</th>
<th>0.5 mg E2/50 mg P4</th>
<th>0.25 mg E2/50 mg P4</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed at 52 weeks</td>
<td>415</td>
<td>284 (68.4)</td>
<td>305 (71.9)</td>
<td>312 (74.1)</td>
<td>151</td>
</tr>
<tr>
<td>Discontinued</td>
<td>131 (31.6)</td>
<td>119 (28.1)</td>
<td>109 (25.9)</td>
<td>143 (33.7)</td>
<td>93</td>
</tr>
<tr>
<td>Adverse event</td>
<td>46 (11.1)</td>
<td>33 (7.8)</td>
<td>34 (8.1)</td>
<td>41 (9.7)</td>
<td>58</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>27 (6.5)</td>
<td>30 (7.1)</td>
<td>26 (6.2)</td>
<td>38 (9.0)</td>
<td>10</td>
</tr>
<tr>
<td>Subject withdrawal</td>
<td>36 (8.7)</td>
<td>42 (9.9)</td>
<td>29 (6.9)</td>
<td>31 (7.3)</td>
<td>17</td>
</tr>
<tr>
<td>Other*</td>
<td>22 (5.3)</td>
<td>14 (3.3)</td>
<td>20 (4.8)</td>
<td>33 (7.8)</td>
<td>13</td>
</tr>
<tr>
<td>VMS substudy</td>
<td>141</td>
<td>149</td>
<td>147</td>
<td>154</td>
<td>135</td>
</tr>
</tbody>
</table>

Screen failures n=3175
Randomized to treatment n=1845
Did not take 1 capsule n=10

Subjects screened for eligibility n=5020

*Other included investigator decision, lack of efficacy, protocol deviation and other.
VMS Frequency and Severity Substudy

- Most TX-001HR doses significantly reduced the frequency and severity of moderate to severe VMS over 12 weeks; statistically significant reductions occurred as early as 4 weeks with the higher doses.
Cholesterol Parameters

- No clinically significant changes in cholesterol levels observed with TX-001HR or placebo.
Cholesterol

- 36 of 1269 women (2.8%) had potentially clinically important cholesterol increases (≥50 mg/dL or above normal levels) at 12 months
  - Comparable between TX-001HR (2.8%) and placebo (3.3%) groups
Triglycride and Glucose Parameters

- No clinically significant changes in triglycerides and glucose levels observed with TX-001HR or placebo
Triglycerides

- 111 of 1269 women (8.7%) had potentially clinically important triglycerides increases (≥50 mg/dL or above normal levels) at 12 months
  - Comparable between TX-001HR (8.9%) and placebo (6.6%) groups

![Triglycerides Increase Graph]

Coagulation Parameters

- No clinically significant changes in antithrombin activity, factor XIV and protein S were observed with TX-001HR compared with placebo.
Coagulation Parameters

- Fibrinogen levels, time for activated partial thromboplastin and prothrombin, and prothrombin INR (ratio of 1) remained similar to baseline at 12 months.

INR: international normalized ratio.
Vascular Disease Outcomes

• Cardiovascular disease
  • Two women experienced “coronary heart disease” adverse events considered not related to treatment
    • Unstable angina (0.5 mg E2/50 mg P4)
    • Angina and coronary artery disease (1 mg E2/100 mg P4)
    • Observed CHD event rate of 2/1684 was less than the expected annual rate of 2-3/1000 in women of this age¹
  • There were no stroke events

• Venous thromboembolism (VTE)
  • One case of deep vein thrombosis (DVT) with 0.5 mg E2/50 mg P4, deemed possibly related to treatment, occurred in a woman with a family history of DVT
    • Observed VTE event rate of 1/1684 was less than the expected annual rate of 1.7/1000 in women of this age²

Conclusions

• After 12 months of treatment with TX-001HR, no clinically meaningful effects on lipid, glucose, or coagulation parameters were observed compared with placebo
  • Observed changes in triglyceride levels, antithrombin activity, factor XIV, and protein S were consistent with oral estrogen therapy
• Although this trial lacked statistical power to assess these outcomes, VTE, cardiovascular disease, and cerebrovascular events were as expected for a menopausal population
• If approved, TX-001HR may provide the first oral E2/P4 combination for the treatment of VMS in menopausal women with a uterus