Progesterone bioavailability for preventing endometrial stimulation with a continuous-combined regimen of TX-001HR (oral estradiol and micronized progesterone capsules)

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Background

• Many postmenopausal women choose hormone therapy (HT) with natural progesterone (P4)

• TX-001HR is an investigational, oral, combined, 17β-estradiol (E2)/micronized P4 softgel capsule being developed for treating moderate-to-severe vasomotor symptoms (VMS) in menopausal women with a uterus
  • In the REPLENISH trial, women randomized to continuous oral TX-001HR (100 mg of P4 with E2 doses of 0.5 or 1 mg, or 50 mg with 0.25 or 0.5 mg) did not have endometrial hyperplasia or cancer with 12 months of use, and had a favourable bleeding profile

• Serum P4 levels required to prevent endometrial hyperplasia with HT have not been well characterized

REPLENISH Trial: Endometrial Hyperplasia and Cumulative Amenorrhea

No endometrial hyperplasia or endometrial malignancies detected with any TX-001HR dose or placebo at 12 months

Hyperplasia rate at 12 months

<table>
<thead>
<tr>
<th>E2/P4</th>
<th>n</th>
<th>Incidence rate</th>
<th>1-sided upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/100 mg</td>
<td>280</td>
<td>0 (0)</td>
<td>1.06%</td>
</tr>
<tr>
<td>0.5 mg/100 mg</td>
<td>303</td>
<td>0 (0)</td>
<td>0.98%</td>
</tr>
<tr>
<td>0.5 mg/50 mg</td>
<td>306</td>
<td>0 (0)</td>
<td>0.97%</td>
</tr>
<tr>
<td>0.25 mg/50 mg</td>
<td>274</td>
<td>0 (0)</td>
<td>1.09%</td>
</tr>
<tr>
<td>Placebo</td>
<td>92</td>
<td>0 (0)</td>
<td>3.20%</td>
</tr>
</tbody>
</table>

Cumulative amenorrhea from cycle 1 to 13 was 56-73% with TX-001HR vs 81% with placebo

>90% had amenorrhea during cycle 13

Objectives

• Characterize serum P4 levels with TX-001HR doses in 2 phase 1 studies
  • Multi-dose 7-day study (2 different doses were investigated)
  • Single-dose study under fasted vs fed conditions
Multi-Dose Study: Design

- Phase 1, open-label, randomized, trial in healthy menopausal women
  - Normal diet: 20%-35% fat
- 2 doses of TX-001HR (both containing 100 mg P4 with 1 mg or 0.5 mg E2) were administered orally, daily for 7 days (steady-state)
- Blood was collected on days 1 and 7 to assess PK parameters for P4
  - Prior to dosing [0-hour]
  - Post-dosing: 20, 40, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours
Food-Effect Study: Design

- Phase 1, open-label, randomized, crossover trial in menopausal women
- TX-001HR dose: 1 mg E2/100 mg P4
- Blood was collected to assess PK parameters for P4 under fasting and fed conditions
  - Prior to dosing [0-hour]
  - Post dosing: 20, 40, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, and 72 hours

- Randomization: n=24
  - Fed: n=12
  - Fasting: n=12
  - Single dose of 1 mg E2/100 mg P4
  - Washout period ≥14 days

- Fasting: ≥10 h
- Fed: 30 min after a high-fat meal [52% fat calories]
Analysis and Statistics

• Samples analyzed for progesterone using validated LC-MS/MS assays
• Multi-dose study
  • LLOQ 0.05 ng/mL; inter-day accuracy 1.76% bias; inter-day precision 4.35% CV
  • \( \text{AUC}_{\text{trap}}, \, \text{C}_{\text{avg}}, \, \text{C}_{\text{max}}, \, t_{\text{max}} \) were assessed for progesterone
  • Summarized descriptively
• Single-dose food study
  • LLOQ 0.1 ng/mL; inter-day accuracy 1.53% bias; inter-day precision 4.53% CV
  • \( \text{AUC}_{0-t}, \, \text{AUC}_{0-\infty}, \, \text{C}_{\text{max}}, \, t_{\text{max}} \) were assessed for progesterone
    • Baseline-adjusted geometric mean reported
  • Fasted treatment served as the reference
  • Tested for bioequivalence with geometric mean ratios and 90% CI

\( \text{AUC}_{\text{trap}} \): area under the concentration-time curve during the dosage interval (\( t \)) calculated using the trapezoidal methods
Multi-Dose Study: Results

• Participants had a mean age of 57.2 years and mean BMI of 25.7 kg/m²
  • 82.5% were White and 17.5% African American
• On Day 7 (pre-dose), $C_{\text{trough}}$ ranged from 0.15–0.17 ng/mL
• After 7 days of dosing with TX-001HR doses containing 100 mg P4
  • Mean P4 serum concentration ranged from 0.55–0.76 ng/mL (Table)

<table>
<thead>
<tr>
<th></th>
<th>1 mg E2/100 mg P4 (n=20)</th>
<th>0.5 mg E2/100 mg P4 (n=20)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progesterone Parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$AUC_{\tau_{\text{trap}}} (h\cdot ng/mL)$</td>
<td>14.1 (9.9)</td>
<td>10.1 (9.4)</td>
</tr>
<tr>
<td>$C_{\max} (ng/mL)$</td>
<td>6.5 (6.2)</td>
<td>3.7 (3.2)</td>
</tr>
<tr>
<td>$t_{\max} (h)$</td>
<td>2.2 (1.5)</td>
<td>2.5 (1.9)</td>
</tr>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$AUC_{\tau_{\text{trap}}} (h\cdot ng/mL)$</td>
<td>18.1 (15.6)</td>
<td>12.2 (11.0)</td>
</tr>
<tr>
<td>$C_{\avg} (ng/mL)$</td>
<td>0.76 (0.65)</td>
<td>0.55 (0.45)</td>
</tr>
<tr>
<td>$C_{\max} (ng/mL)$</td>
<td>11.3 (23.1)</td>
<td>4.4 (5.7)</td>
</tr>
<tr>
<td>$t_{\max} (h)$</td>
<td>2.6 (1.5)</td>
<td>2.9 (2.3)</td>
</tr>
</tbody>
</table>

*n=17 at Day 7.

The LLOQ of the LC-MS/MS assay for progesterone was 0.050 ng/mL.
Multi-dose Study Findings

• No statistical difference in P4 levels or PK with E2 doses of 1 mg or 0.5 mg
• Accumulation ratio of 1.4 for Day 7 AUC/Day 1 AUC
Food-Effect Study: Results

- Participants had a mean age of 57.5 years and mean BMI of 26.9 kg/m²
  - 71% were White and 25% African American
- In the fed versus fasted state, ratios were significantly higher for P4 AUC₀⁻ᵗ and Cₘₐₓ
  - For bioequivalency, ratio had to be within 90% CI

Baseline-adjusted PK Parameters

<table>
<thead>
<tr>
<th>Progesterone (P₄)</th>
<th>Fed</th>
<th>Fasting</th>
<th>Fed/Fasting Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀⁻ᵗ (ng·h/mL)</td>
<td>6.45</td>
<td>3.54</td>
<td>1.8</td>
</tr>
<tr>
<td>AUC₀⁻∞ (ng·h/mL)</td>
<td>6.72</td>
<td>5.26</td>
<td>1.3</td>
</tr>
<tr>
<td>Cₘₐₓ (ng/mL)</td>
<td>2.50</td>
<td>0.92</td>
<td>2.7</td>
</tr>
<tr>
<td>tₘₐₓ (h)</td>
<td>2.48</td>
<td>2.64</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Data expressed as baseline-adjusted geometric means
Food-Effect Study: Serum Progesterone

Baseline-Adjusted Serum Progesterone

Mean Progesterone Concentration (ng/mL) vs. Time post-dose (hour)

- Fed
- Fasting
Conclusion

• In the 7-day, multi-dose study, oral TX-001HR with 100 mg P4 resulted in

  • \( \text{AUC}_\tau \text{trap} \) of 10.1–18.1 h·ng/mL
  • \( C_{\text{avg}} \) of 0.55–0.76 ng/mL
  • \( C_{\text{max}} \) of 3.7–11.3 ng/mL

• These systemic P4 levels result in adequate endometrial protection from hyperplasia with continuous-combined E2/P4 (TX-001HR) as observed in the REPLENISH trial,\(^1\) while improving VMS

• In the single-dose, food study, P4 bioavailability was enhanced with food by approximately 2 fold, consistent with other studies of natural P4 (e.g., Prometrium)\(^2\)

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Discussion

• P4 in TX-001HR, by continuous delivery, may protect the endometrium by downregulating endometrial estrogen receptors and decreasing mitotic activity
• This effect of decreasing estrogen action may prevent endometrial hyperplasia and may decrease endometrial bleeding