**Introduction**

- Vasomotor symptoms (VMS) in menopausal women are effectively treated with hormone therapy (HT) reducing hot flush frequency and severity.
- Reductions in VMS frequency of 50% to 86% from baseline, or 5.5 to 9.0 hot flushes per day, have been reported in some randomized controlled trials. However, the clinical relevance of these findings is often unknown.

**Methods**

- **REPLENISH (NCT01942668)** was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that evaluated TX-001HR in menopausal women aged 40–65 years; BMI ≤34 kg/m² with a uterus.
- 12-week efficacy substudy for the treatment of vasomotor symptoms:
  - 1-year endometrial and general safety analyses
  - Women with moderate-to-severe hot flushes (≥7/day or ≥50/wk) were randomized to daily E2/P4 (mg/mg) 1/100, 0.5/100, 0.5/50, 0.25/50 or placebo (VMS substudy, n=726); others were randomized to E2/P4 doses only for endometrial assessment (MITT-VMS population).

**Results**

- **Clinical meaningfulness of treatment** was assessed using the Clinical Global Impression (CGI) scale. Participants answered the following question: “Compared to your condition at admission to the study, how much has it changed?”
- **Calculation of clinical meaningfulness thresholds** showed that the difference between treatment groups was statistically significant for reductions of ≥25 for MCID and ≥39 for CID for week 12 (Figure 4A) and reductions of ≥25 for MCID and ≥39 for CID for week 12 (Figure 4B).
- **Clinical meaningfulness** of TX-001HR was associated with clinically meaningful improvements in VMS frequency in menopausal women.

**Concluding Remarks**

- TX-001HR provided clinically meaningful improvements in VMS frequency in menopausal women as determined by CGI.
- The results of this analysis extend the primary efficacy results of the REPLENISH trial, which showed significant improvements in the frequency and severity of moderate-to-severe vasomotor symptoms (VMS) in menopausal women (age 40–65 years; BMI ≤34 kg/m²) with a uterus.
- Clinically important differences in VMS reductions for moderate-to-severe VMS frequency, regardless of treatment, were measured using anchor-based CGI nonparametric discriminant analyses utilizing bootstrapping methods.
- Analyses were performed in the MITT-VMS population.
- Each E2/P4 dose was compared with placebo using the Fisher’s Exact test at weeks 4 and 12.

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**References**

- Palatin Technologies, Symbio Research, and TherapeuticsMD; has also served (within the past year, or current) on the speaker’s bureaus of Novo Nordisk, Shionogi, and Valeant; and is a stockholder of TherapeuticsMD.
- Much worse
- Much improved
- Potential Responses
- No change or worse
- Minimally improved
- 0.5 mg E2/100 mg P4
- 0.25 mg E2/50 mg P4
- 1 mg E2/100 mg P4
- 0.5 mg E2/50 mg P4

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**Figure 1.** Reductions in moderate-to-severe VMS frequency in the REPLENISH trial

**Figure 2.** Study Design

**Figure 3.** Proportion of women who rated their condition as very much or much improved (CGI response rate)

**Figure 4.** Clinical meaningfulness analysis at (A) week 4 and (B) week 12

**Figure 5.** CGI-based CID and MCID analysis at (A) Week 4 and (B) Week 12

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**Table 1.** CGI Ratings

<table>
<thead>
<tr>
<th>CGI Rating</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Much improved</td>
<td>Clinically meaningful</td>
<td>2</td>
</tr>
<tr>
<td>Moderately improved</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Minimally improved</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>No change</td>
<td></td>
<td>-1</td>
</tr>
<tr>
<td>Worsened</td>
<td></td>
<td>-2</td>
</tr>
</tbody>
</table>

**Figure 5.** Density Estimates at Week 4

**Figure 6.** Density Estimates at Week 12

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**Table 2.** Demographics and baseline characteristics of the MITT-VMS population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>E2/P4 (mg/mg)</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>26.6 ± 3.9</td>
<td>26.6 ± 3.9</td>
<td>0.010</td>
</tr>
<tr>
<td>Weekly hot flush frequency</td>
<td>2.51 ± 0.26</td>
<td>2.51 ± 0.26</td>
<td>0.100</td>
</tr>
</tbody>
</table>

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**Table 3.** Co-primary efficacy endpoints measured at 4 and 12 weeks demonstrated statistically significant reductions in hot flush frequency with most E2/P4 doses compared with placebo (Figure 1)

<table>
<thead>
<tr>
<th>Week</th>
<th>E2/P4 (mg/mg)</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1 mg E2/100 mg P4</td>
<td>1 mg E2/100 mg P4</td>
<td>0.000</td>
</tr>
<tr>
<td>12</td>
<td>1 mg E2/100 mg P4</td>
<td>1 mg E2/100 mg P4</td>
<td>0.000</td>
</tr>
</tbody>
</table>

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<td>0.000</td>
</tr>
</tbody>
</table>

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**Table 5.** Clinical meaningfulness of treatment was assessed using the Clinical Global Impression (CGI) scale. Participants answered the following question: “Compared to your condition at admission to the study, how much has it changed?”

- **Potential CGI responses** were then converted to CGI rating responses to determine clinical meaningfulness.
- Each E2/P4 dose was compared with placebo using the Fisher’s Exact test at weeks 4 and 12.