TX-001HR Improved the Medical Outcomes Study-Sleep (MOS-Sleep) questionnaire in Menopausal Women with Vasomotor Symptoms

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• **Speaker’s bureau:** AMAG, Pfizer, and Valeant
Menopausal VMS Treatment

• Vasomotor symptoms (VMS) in menopausal women can
  • Be bothersome\textsuperscript{1-3}
  • Negatively impact quality of life,\textsuperscript{1,4} sleep,\textsuperscript{1,5} and work productivity\textsuperscript{4,6}

• REPLENISH trial
  • TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational combination of 17β-estradiol and progesterone in a single oral softgel capsule
  • One secondary objective was to evaluate the effects of four TX-001HR (E2/P4) doses versus placebo on sleep parameters when used for the treatment of moderate-to-severe VMS

E2: estradiol; P4: progesterone.

Study Design: Randomization

VMS substudy (12 wks)
- \( \geq 7/\text{day or } \geq 50/\text{week} \) 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
- 1.0 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 sleep parameters using the Medical Outcomes Study (MOS)-Sleep Questionnaire
Medical Outcomes Study (MOS)-Sleep Questionnaire

• MOS-Sleep is a 12-item questionnaire measuring 6 sleep dimensions over the past 4 weeks
  • The last 4 items* were scored using a 6-item Likert scale ranging from “All of the time” to “None of the time”

<table>
<thead>
<tr>
<th>Sleep Dimensions</th>
<th>Subscales (derived from sleep dimensions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Initiation (time to fall asleep)</td>
<td>• Sleep Problems Index I (short form)</td>
</tr>
<tr>
<td>• Quantity (hours of sleep each night)</td>
<td>• Sleep Problems Index II (long form)</td>
</tr>
<tr>
<td>• Maintenance*</td>
<td>• Sleep disturbance</td>
</tr>
<tr>
<td>• Respiratory problems*</td>
<td>• Sleep somnolence</td>
</tr>
<tr>
<td>• Perceived adequacy*</td>
<td>• Snoring</td>
</tr>
<tr>
<td>• Somnolence*</td>
<td>• Sleep shortness of breath or headache</td>
</tr>
</tbody>
</table>

• MOS-Sleep questionnaire was administered at baseline, week 12 and months 6 and 12

• Change from baseline in total and subscale scores were analyzed for each treatment versus placebo at each time point in the MITT population
### Disposition and Demographics

- 69% of women completed at 52 weeks
- Mean age: 55 years (40–66)
- Mean BMI: 27 kg/m²
- 65% were white and 32% black

#### Randomized to treatment

<table>
<thead>
<tr>
<th>E2/P4 (mg)</th>
<th>MITT population n=1833</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 / 100</td>
<td>416 (68.2)</td>
</tr>
<tr>
<td>0.5 / 100</td>
<td>422 (71.9)</td>
</tr>
<tr>
<td>0.5 / 50</td>
<td>421 (74.1)</td>
</tr>
<tr>
<td>0.25 / 50</td>
<td>423 (66.2)</td>
</tr>
</tbody>
</table>

#### Placebo

- 151 (61.2)

MITT: modified intent-to-treat population.
Improvements in MOS-Sleep Total Score

• All doses of TX-001HR significantly improved the MOS-Sleep total score versus placebo at week 12 and months 6 and 12
  • Except for those treated with the lowest dose at week 12
• Total scores ranged from 43.2–48.1 at baseline and were 27.5–29.4 with TX-001HR and 37.4 with placebo at month 12

![Graph showing mean reduction from baseline over months for different doses of TX-001HR compared to placebo.](image-url)

*\(P<0.05\); †\(P<0.01\); ‡\(P<0.001\) vs placebo.
Improvements in Sleep Disturbance Subscale

- Sleep disturbance subscale significantly decreased from baseline with TX-001HR versus placebo at all timepoints
  - Except for the lowest TX-001HR dose at week 12

*P<0.05; †P<0.01; ‡P<0.001 vs placebo.
Improvements in Sleep Problems Index I Subscale

• All doses of TX-001HR significantly improved the Sleep Problems Index I subscale from baseline versus placebo to all timepoints.

Sleep problems index I based on
How often during the past 4 weeks did you...
• Get enough sleep to feel rested upon waking?
• Awaken short of breath or with a headache?
• Have trouble falling asleep?
• Awaken and have trouble falling asleep again
• Have trouble staying awake during the day?
• Get the amount of sleep you needed?

*P<0.05; †P<0.01; ‡P<0.001 vs placebo.
Improvements in Sleep Problems Index II Subscale

- All doses of TX-001HR significantly improved the Sleep Problems Index II subscale from baseline versus placebo to all timepoints
  - Except the lowest TX-001HR dose at week 12

Sleep Problems Index II

Same questions as the Sleep problems index I but also include:
- How often during the past 4 weeks did you...
  - Feel that your sleep was not quiet?
  - Feel drowsy or sleepy during the day
  - How long did it usually take to fall asleep?

*P<0.05; †P<0.01; ‡P<0.001 vs placebo.
Improvements in Sleep Somnolence Subscale

- Sleep somnolence subscale significantly improved from baseline with TX-001HR doses 0.5 mg E2/100 mg P4 and 0.5 mg E2/50 mg P4 compared with placebo at month 12
  - TEAE incidence of somnolence was low (0.2% to 1.2%) with TX-001HR
- TX-001HR had no effects on the snoring subscale, or the sleep shortness of breath or headache subscale

**Mean reduction from baseline**

<table>
<thead>
<tr>
<th>Months</th>
<th>1.0 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>
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</thead>
<tbody>
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</tbody>
</table>

*P<0.05; †P<0.01 vs placebo.

TEAE: Treatment-emergent adverse events.
Conclusions

• All doses of TX-001HR significantly improved sleep parameters typically associated with menopause from baseline up to 12 months compared with placebo
  • Some improvements with the lowest dose was not significant at 12 weeks
  • The reported incidence of somnolence was also very low
• If approved, TX-001HR may provide the first oral combination of E2/P4 for treating moderate-to-severe VMS and could represent a new treatment option for menopausal women currently using unapproved and unregulated compounded bioidentical HT