17β-Estradiol/Progesterone in a Single, Oral, Softgel Capsule (TX-001HR) Significantly Increased the Number of VMS Symptom-free Days in the REPLENISH Trial

Andrew M Kaunitz, MD1; Ginger D Constantine, MD2; Brian Bernick, MD3; Sebastian Mirkin, MD3

1University of Florida College of Medicine-Jacksonville, Jacksonville, FL; 2EndoRheum Consultants, LLC, Malvern, PA; 3TherapeuticsMD, Boca Raton, FL

VMS: vasomotor symptoms.
Disclosures

- **Consultant/advisory boards (current):** AMAG Pharmaceuticals, Bayer Healthcare, Mithra, and Shionogi Inc
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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}
- VMS can be effectively treated with hormone therapy (HT), which reduces hot flush frequency and severity
- No HT formulation combining 17\(\beta\)-estradiol and progesterone in a single oral capsule has yet been approved by the FDA
- TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational combination of 17\(\beta\)-estradiol and progesterone in a single, oral, softgel capsule\textsuperscript{7}

REPLENISH Trial

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

- Secondary endpoints
  - Responder rates: Women with at least 50% or 75% reductions in their moderate to severe VMS frequency (prespecified)
  - Number of days with no moderate to severe VMS (post hoc)
  - Proportion of women with no severe VMS (post hoc)

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 (no placebo)

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

Disposition and Demographics

- 89% completed at least 12 weeks
- Mean age of 54.6 years (40–65)
- Mean BMI of 26.6 kg/m²
- 67% were white; 31% African American

Subjects screened for eligibility n=5020

Screen failures n=3175

Randomized to treatment n=1845

Did not take 1 capsule n=10

Population, n (%)
MITT VMS
Completed at 12 weeks
1 mg E2/100 mg P4
141
125 (88.7)

0.5 mg E2/100 mg P4
149
135 (90.6)

0.5 mg E2/50 mg P4
147
130 (88.4)

0.25 mg E2/50 mg P4
154
139 (90.3)

Placebo
135
118 (87.4)

MITT: modified intent-to-treat population.
VMS Frequency and Severity

- 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 3 weeks with the higher doses.

**Weekly Reduction in VMS Frequency**

- 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

**Weekly Improvement in VMS Severity**

- 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

*P<0.05 from *Weeks 3–12; †Weeks 4–12; ‡Weeks 6-12 vs placebo.

Responder Rates

• Significantly more women were responders at week 12 with TX-001HR than with placebo

**Women with ≥50% or ≥75% Reductions in Moderate to Severe VMS Frequency at Week 12**

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<tr>
<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>
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*Responder rates: Women with at least 50% or 75% reductions in their moderate to severe VMS

*\(P<0.05; \, \dagger P<0.01; \, \ddagger P\leq0.001\) vs placebo
Number of days per week without moderate to severe VMS was significantly higher with all TX-001HR doses than placebo at week 12, as early as week 6.

P<0.05 from *Weeks 3–12; †Weeks 4–12; ‡Weeks 6-12 vs placebo.
Symptoms-free Days

- Significantly more women (43–56%) who took TX-001HR had no severe VMS at 12 weeks compared with 26% who took placebo.

Severe hot flushes: sensation of heat with sweating that causes cessation of activity.

*P≤0.01; †P<0.001 vs placebo.
Conclusions

• As previously reported, 1 mg E2/100 mg P4 and 0.5 mg E2/100 mg P4 doses of TX-001HR provided significant and clinically meaningful improvements in VMS frequency and severity at weeks 4 and 12\(^1\)
  • The 100 mg and 50 mg continuous doses of P4 protected the endometrium from 1 mg, 0.5 mg and 0.25 mg E2\(^1\)

• More women taking TX-001HR versus placebo had 50% and 75% reductions in their moderate to severe VMS frequency

• TX-001HR significantly increased the number of moderate to severe VMS symptom-free days versus placebo

• If approved, TX-001HR may be a treatment option for women with moderate to severe VMS and an intact uterus, including those who use compounded HT that has not undergone FDA review for safety and efficacy