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

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VMS: vasomotor symptoms.

# Disclosures

- **Consultant/advisory boards (current)**: AMAG Pharmaceuticals, Bayer Healthcare, Mithra, and Shionogi Inc
- **Research support** (to the University of FL): Bayer Healthcare and TherapeuticsMD

# Menopausal VMS Treatment

- Vasomotor symptoms (VMS) in menopausal women can
  - Be bothersome[1-3]
  - Negatively impact quality of life,[1,4] sleep,[1,5] and work productivity[4,6]
- VMS can be effectively treated with hormone therapy (HT), which reduces hot flush frequency and severity
- No HT formulation combining 17β-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 17β-estradiol and progesterone in a single, oral, softgel capsule[7]

**1.** Blumel JE, et al. *Menopause* 2011;18:778-785. **2.** Hunter MS, et al. *BJOG* 2012;119:40-50. **3.** Duffy OK, et al. *BJOG* 2012;119:554-564. **4.** Whiteley J, et al. *Menopause* 2013;20:518-524. **5.** Blumel JE, et al. *Maturitas* 2012;72:359-366. **6.** Kleinman NL, et al. *J Occup Environ Med* 2013;55:465-470. **7.** Lobo RA et al. *Obstet Gynecol* 2018;132:161-170.

# 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*)

Lobo RA et al. *Obstet Gynecol* 2018;132:161-170.

# 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

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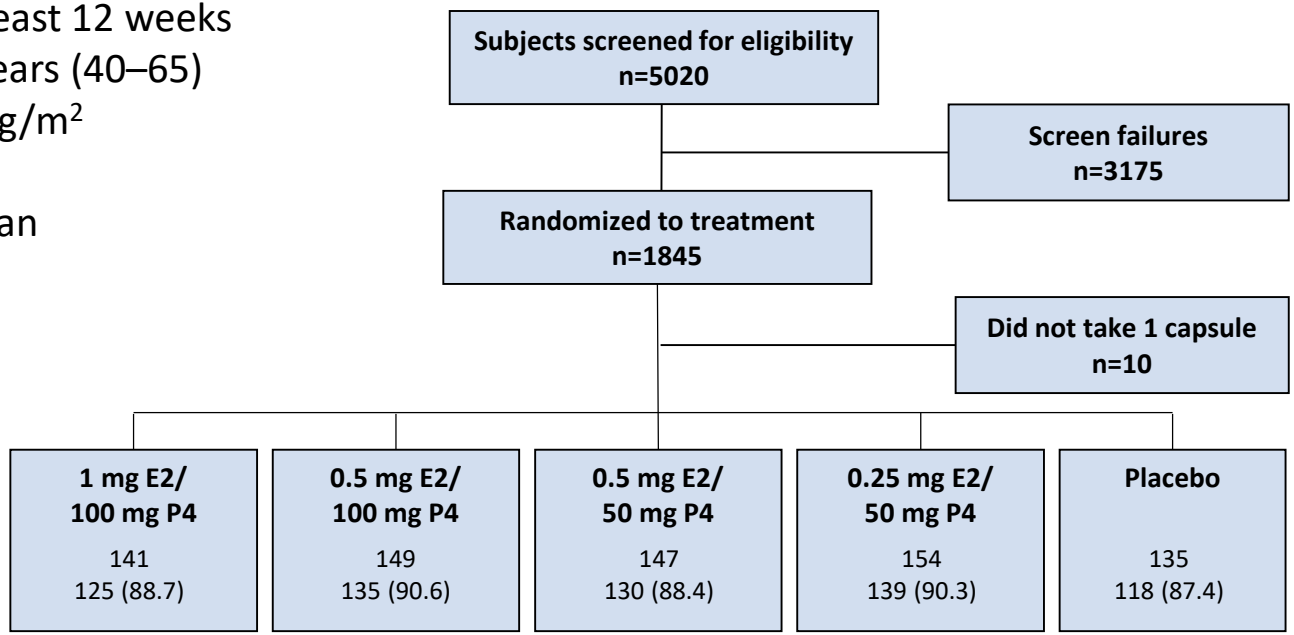
# Disposition and Demographics

- 89% completed at least 12 weeks
- Mean age of 54.6 years (40–65)
- Mean BMI of 26.6 kg/m$^2$
- 67% were white;
  31% African American



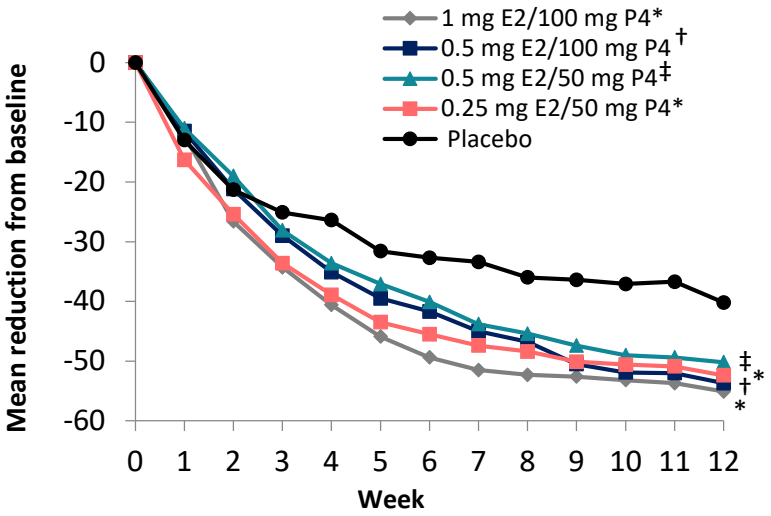

MITT: modified intent-to-treat population.

Lobo RA et al. *Obstet Gynecol* 2018;132:161-170.

# VMS Frequency and Severity

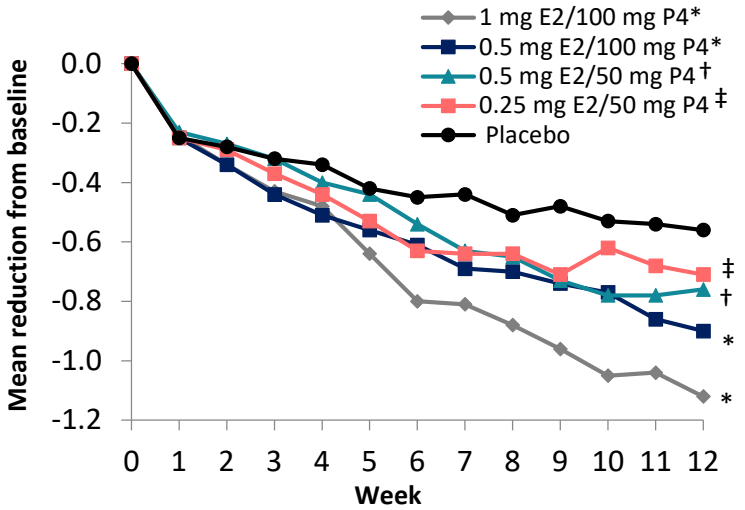
- Most TX-001HR doses significantly reduced the frequency and severity of moderate to severe VMS over 12 weeks; statistically significant reductions occurred as early as 3 weeks with the higher doses

**Weekly Reduction in VMS Frequency**




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

**Weekly Improvement in VMS Severity**

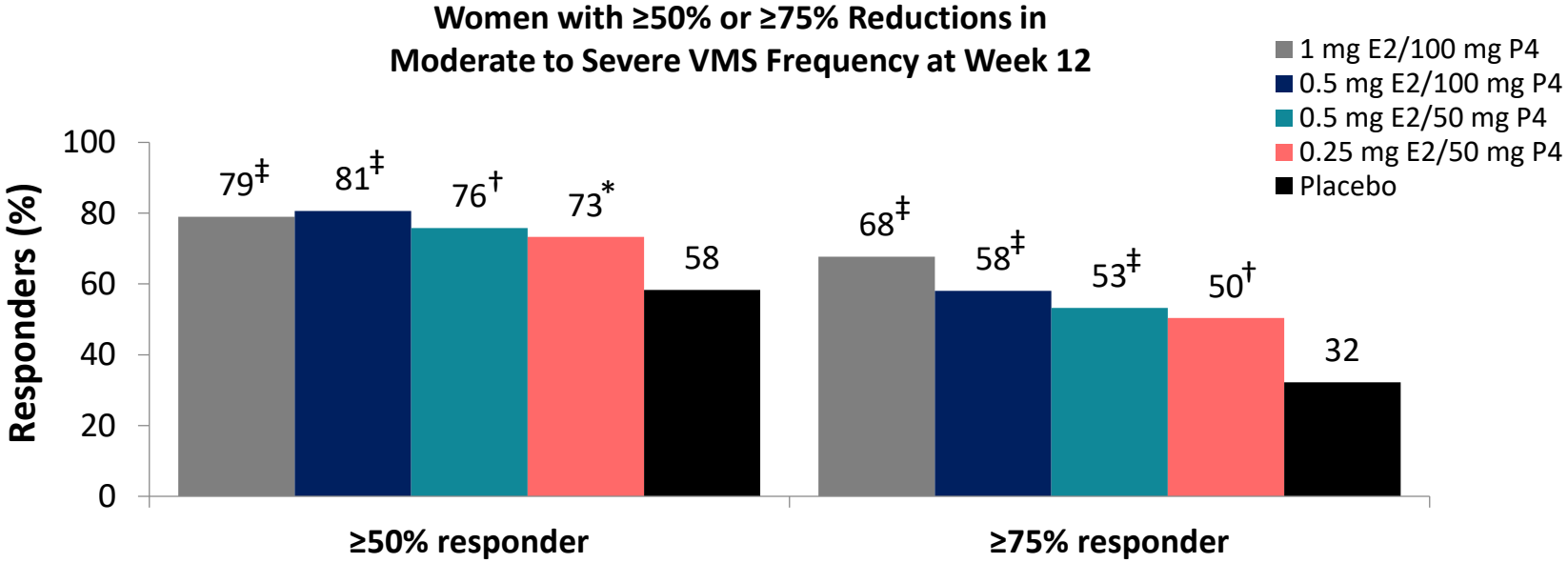



*P*<0.05 from *Weeks 3–12; †Weeks 7, 9–12; ‡Weeks 6, 7, 9 vs placebo.

Lobo RA et al. *Obstet Gynecol* 2018;132:161-170.

# Responder Rates

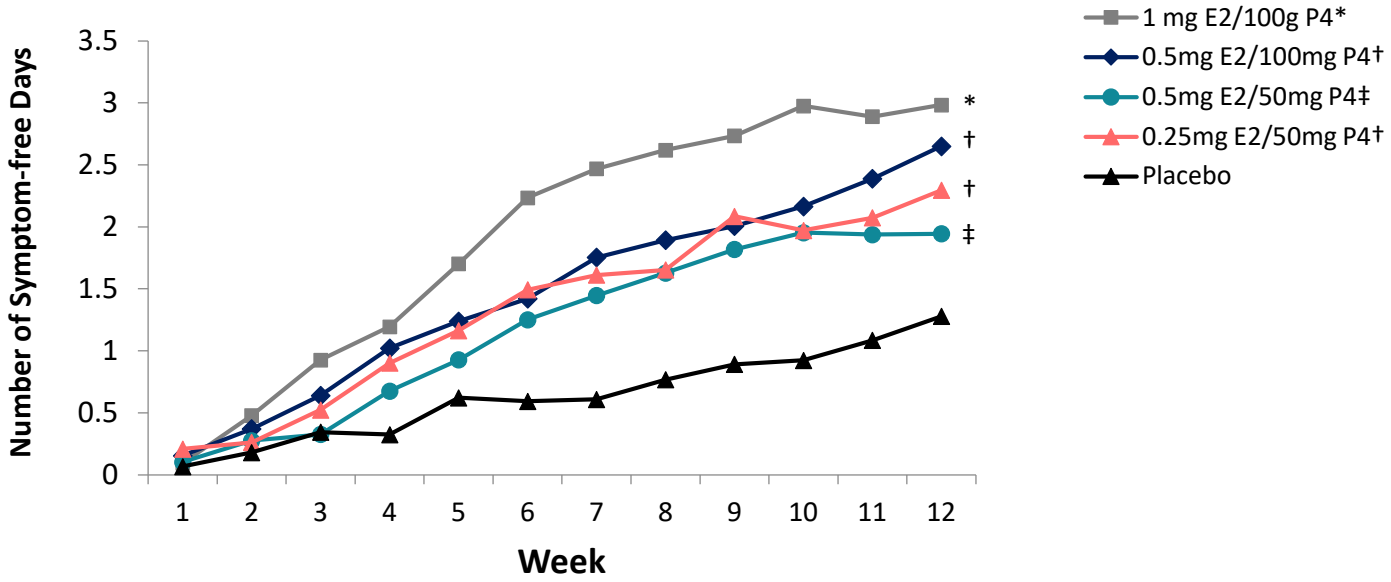
- Significantly more women were responders at week 12 with TX-001HR than with placebo




Responder rates: Women with at least 50% or 75% reductions in their moderate to severe VMS
*$P<0.05$; †$P<0.01$; ‡$P\leq0.001$ vs placebo

# Moderate to Severe VMS-free Days

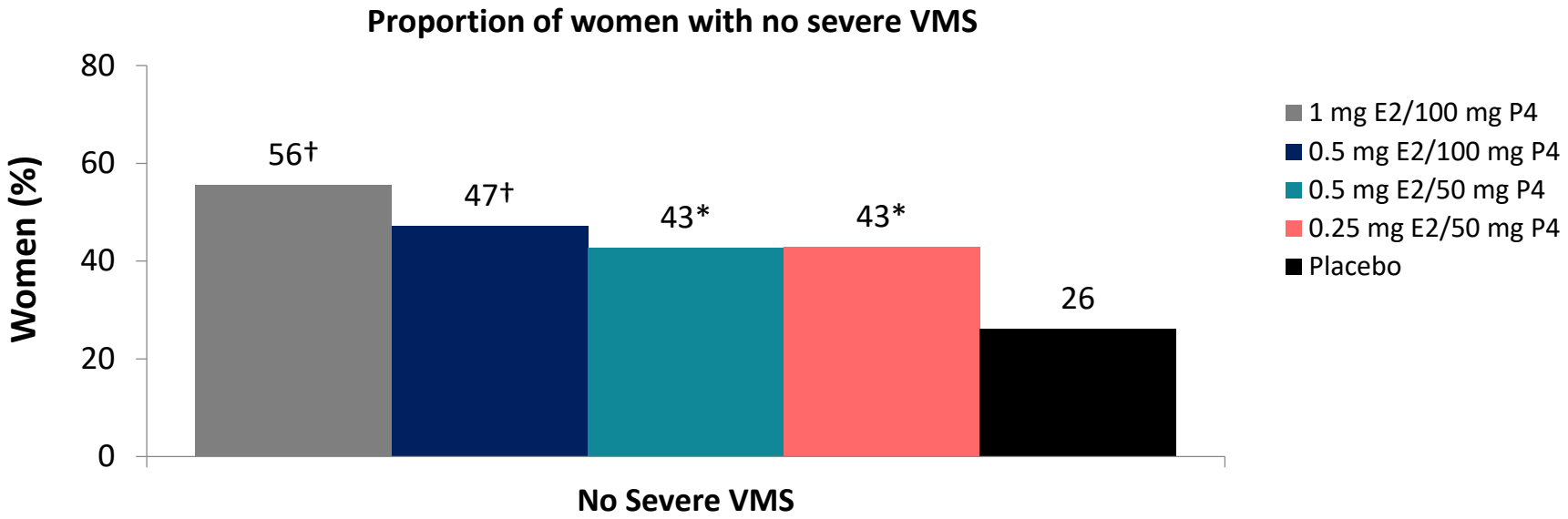
- Number of days per week without moderate to severe VMS was significantly higher with all TX-001HR doses than placebo at week 12, as early as week 6




*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.
*$P \leq 0.01$; †$P < 0.001$ 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

**1.** Lobo RA et al. *Obstet Gynecol* 2018;132:161-170.