REPLENISH trial: 17β-Estradiol and Progesterone Combined in a Single Capsule (TX-001HR) Significantly Improved Moderate-to-Severe Vasomotor Symptoms in Postmenopausal Women

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Background

- Use of compounded bio-identical HT (estradiol and progesterone) has become highly prevalent in the US since the 2002 WHI report[1]
  - An estimated 1 to 2.5 million US women use unapproved compounded products,[1,2] representing up to 21 to 39 million prescriptions annually[1]
  - Some compounded products may be associated with increased risks[3]
  - No HT products combining 17β-estradiol and progesterone are FDA-approved
- TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational combination of naturally occurring 17β-estradiol and progesterone (sometimes referred to as bio-identical hormones) in a single oral softgel capsule

HT: hormone therapy.

1. Pinkerton J and Santoro N. *Menopause* 2015;22:926-936. **2.** Pinkerton J and Constantine G. *Menopause* 2016;23:359-367. **3.** Pinkerton J and Pickar JH. *Menopause.*2015;23:215-223.

REPLENISH Trial: Objective and Design

- **Objective:** To evaluate the efficacy and safety of four TX-001HR (estradiol [E2] combined with progesterone [P4]) doses versus placebo for the treatment of moderate-to-severe vasomotor symptoms
- **Design:** Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in postmenopausal women with an intact uterus (NCT01942668)
  - 1-year endometrial safety study and 12-week efficacy substudy for the treatment of vasomotor symptoms

Key Inclusion Criteria

- Healthy postmenopausal women aged 40-65 years
- Intact uterus
- Body mass index ≤34 kg/m^2
- Vasomotor symptoms associated with menopause
- Acceptable endometrial biopsy results

<u>Vasomotor Symptom (VMS) Substudy</u>

- ≥7/day or ≥50/week moderate-to-severe hot flushes

Key Exclusion Criteria

- History of endometrial hyperplasia, melanoma, or uterine/ endometrial, breast, or ovarian cancer
- History of thrombosis of deep veins/arteries or thromboembolic disorder, coronary artery or cerebrovascular disease, chronic liver or kidney dysfunction/disorder, malabsorption disorder, gallbladder dysfunction/disorders, diabetes, thyroid disease or any other endocrine disorder
- Prior use of estrogen-, progestogen-, androgen-, SERM products for variable period of time depending on the formulation
- Medications that are known to induce or affect estrogen and/or progestogen drug metabolism or activity (≤4 weeks)

Study Design: Randomization

- Postmenopausal women (40-65 years) were randomized to daily, oral E2/P4 groups or placebo

Randomization	Treatment Groups*
• Women with moderate-to-severe hot flushes were randomized 1:1:1:1:1 to one of four E2/P4 doses or placebo (included in VMS substudy and endometrial study) • Women not qualifying for the VMS substudy were randomized 1:1:1:1 to one of four E2/P4 doses (endometrial study)	• 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

*All women took 2 capsules in a double-blind, double dummy manner to maintain study blinding as 2 different capsule sizes were necessary to accommodate the different doses.

- All women completed a daily diary on the frequency and severity of their VMS through week 12; MENQOL scores were also obtained.

E2: estradiol; P4: progesterone; VMS: vasomotor symptoms.

REPLENISH Trial: Study Endpoints

Endpoints		Description
Efficacy • VMS substudy	**4 co-primary endpoints**	**VMS frequency (moderate-to-severe)** • Mean change from baseline to week 4 • Mean change from baseline to week 12 **VMS severity** • Mean change from baseline to week 4 • Mean change from baseline to week 12
	Secondary	• Mean change in frequency and severity of moderate-to-severe VMS from baseline for each week up to week 12
Safety • All women who took ≥1 capsule	**Primary**	• Incidence of endometrial hyperplasia with up to 12 months of treatment (in women with endometrial biopsies) • **Results presented on poster LB SUN 07**
	Secondary	• Incidence of AEs and serious AEs

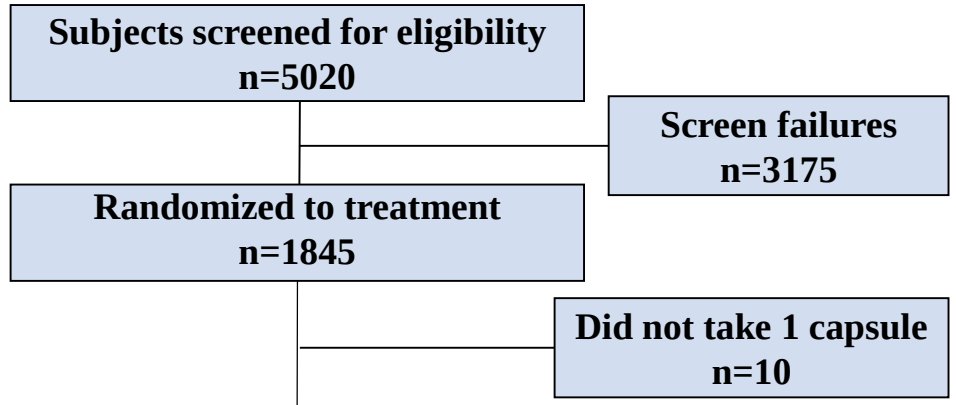
AEs: adverse events; VMS: vasomotor symptoms.

Statistical Analyses

- Efficacy analyses were performed on the modified intent-to-treat (MITT) population of the VMS substudy
  - MITT VMS substudy included women who took ≥1 dose of study treatment, had ≥5 days of VMS diary data at baseline, and ≥4 days of VMS diary data for 1 on-treatment week
  - Each TX-001HR dose was compared with placebo and tested for the 4 co-primary efficacy endpoints at alpha level 0.05 (two-tailed) using a mixed model repeated measures (MMRM) analysis
- Endometrial safety was analyzed in women who took ≥1 capsule, had an acceptable biopsy at baseline, and had a biopsy at month 12 or had a diagnosis of endometrial hyperplasia prior to month 12
- AEs and serious AEs were descriptively summarized in all women who took ≥1 capsule (safety population)

Disposition

- 89% of women completed the VMS substudy at 12 weeks



Population, n (%)	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
MITT VMS	141	149	147	154	135
Completed at 12 weeks	125 (88.7)	135 (90.6)	130 (88.4)	139 (90.3)	118 (87.4)
Safety	415	424	421	424	151
Completed at 52 weeks	284 (68.4)	305 (71.9)	312 (74.1)	281 (66.3)	93 (61.6)
Discontinued	131 (31.6)	119 (28.1)	109 (25.9)	143 (33.7)	58 (38.4)
Adverse event	46 (11.1)	33 (7.8)	34 (8.1)	41 (9.7)	10 (6.6)
Lost to follow-up	27 (6.5)	30 (7.1)	26 (6.2)	38 (9.0)	17 (11.3)
Subject withdrawal	36 (8.7)	42 (9.9)	29 (6.9)	31 (7.3)	13 (8.6)
Other*	22 (5.3)	14 (3.3)	20 (4.8)	33 (7.8)	18 (11.9)
Endometrial Safety	280	303	306	274	92

*Other included investigator decision, lack of efficacy, protocol deviation and other.

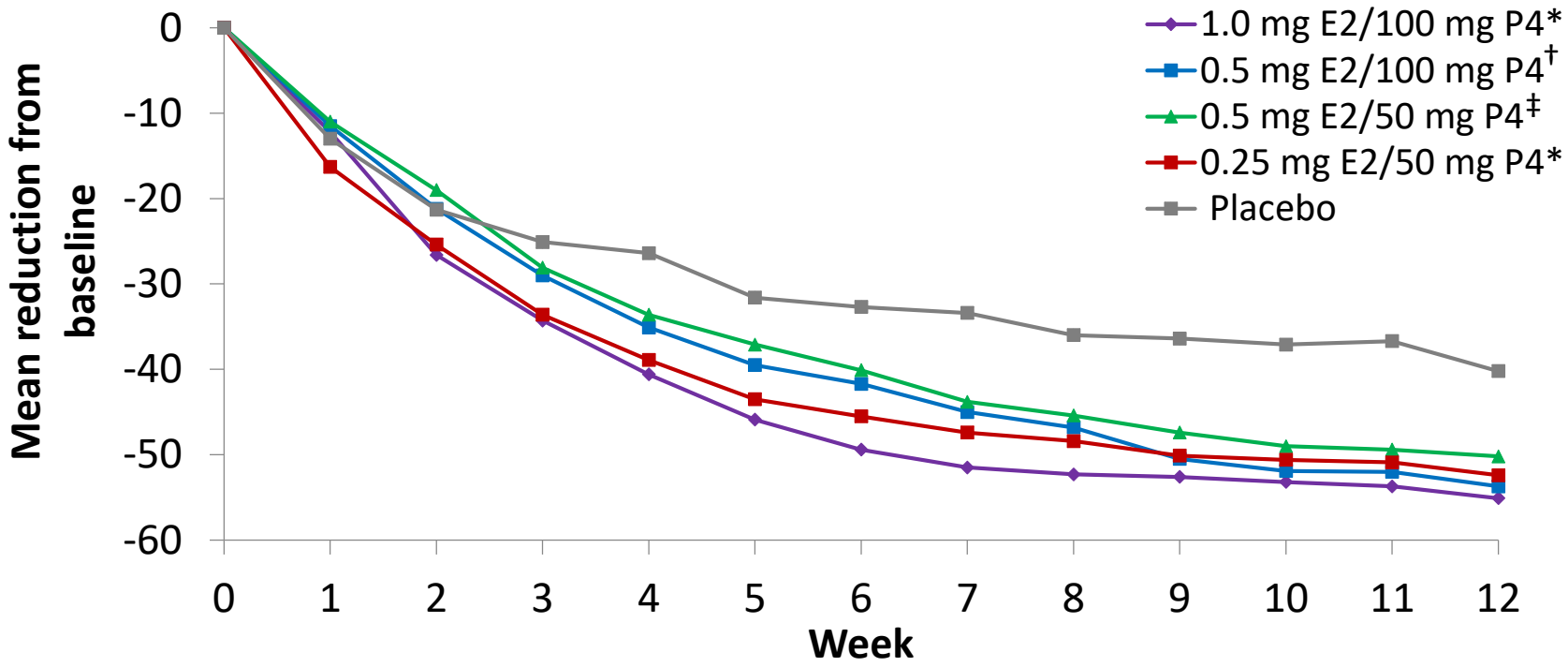
Demographics of VMS Substudy

- Women had a mean age of 55 years (range, 40 to 65) and a mean BMI of 27 kg/m^2
- 67% of the women were white and 31% black

Parameter	Estradiol/Progesterone				Placebo
	1 mg/ 100 mg	0.5 mg/ 100 mg	0.5 mg/ 50 mg	0.25 mg/ 50 mg	
n	141	149	147	154	135
Age, y Mean ± SD	54.7 ± 4.8	54.9 ± 4.5	54.8 ± 4.6	54.5 ± 3.8	54.3 ± 4.3
Race, n (%) White Black Other	 95 (67.4) 45 (31.9) 1 (0.7)	 99 (66.4) 48 (32.2) 2 (1.3)	 99 (67.3) 43 (29.3) 5 (3.4)	 102 (66.2) 48 (31.2) 4 (2.5)	 91 (67.4) 41 (30.4) 3 (2.2)
BMI, kg/m^2 Mean ± SD	26.5 ± 3.9	27.1 ± 4.3	26.6 ± 3.9	26.4 ± 4.0	26.6 ± 3.8

Weekly Reduction in VMS Frequency

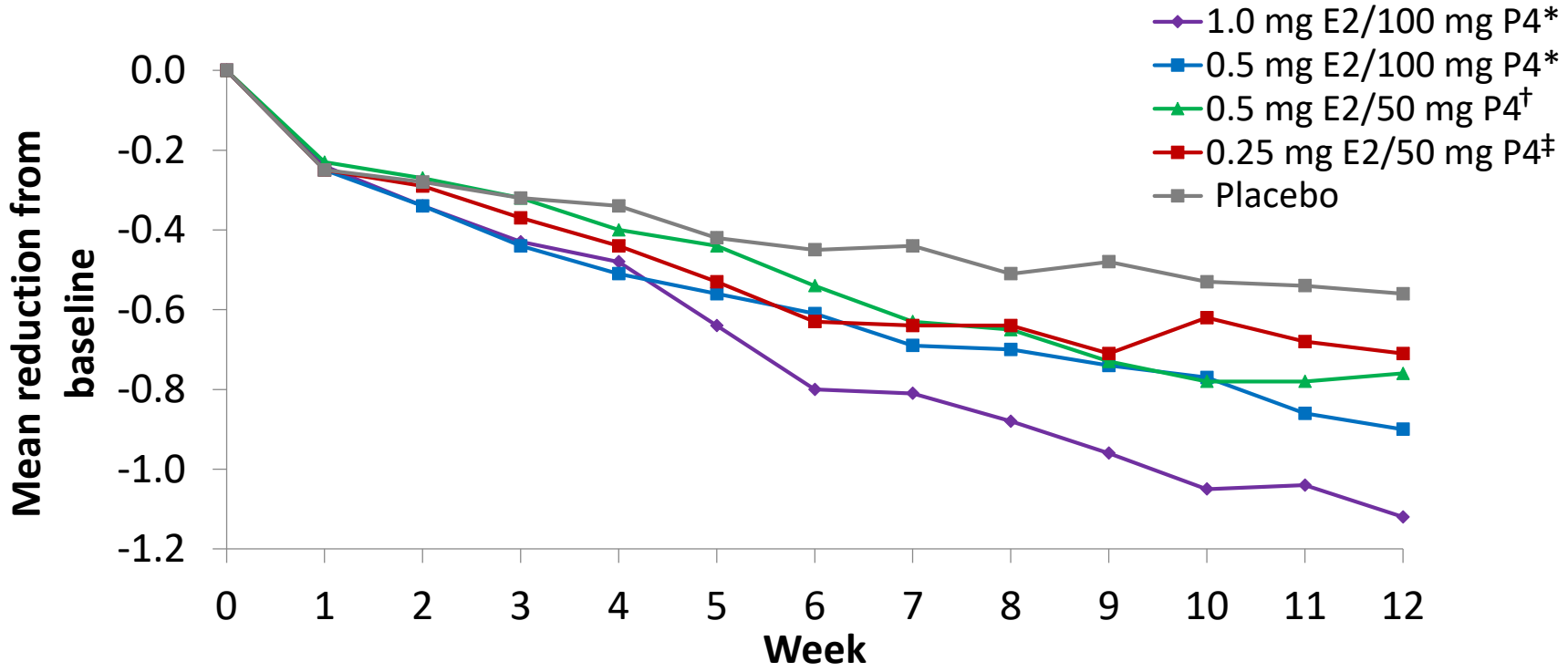
- All TX-001HR doses provided statistically and clinically significant reduction in the weekly frequency of moderate-to-severe VMS from baseline at weeks 4 and 12 compared with placebo
  - Except for 0.5 mg E2/50 mg P4, which reached significance at week 6



Significantly different from placebo (P<0.05) from *Weeks 3–12; †Weeks 4–12; ‡Weeks 6-12.

Weekly Improvement in VMS Severity

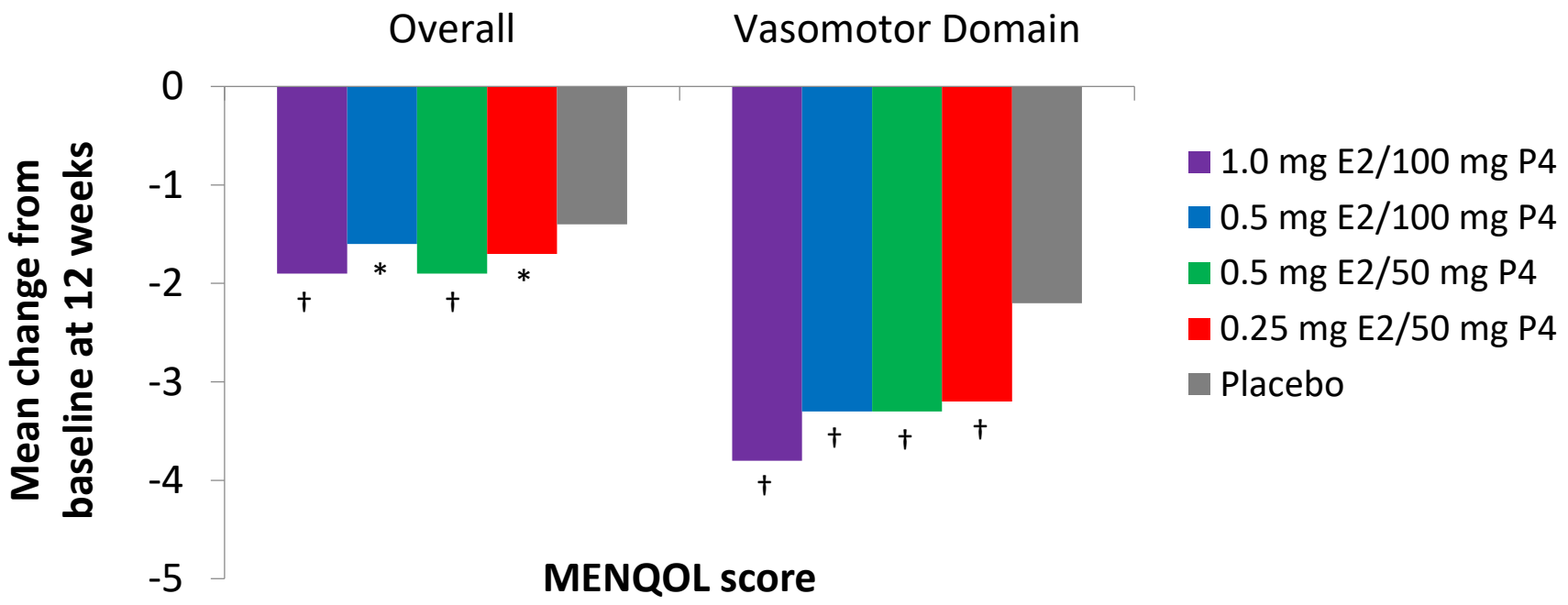
- Doses 1.0 mg E2/100 mg P4 and 0.5 mg E2/100 mg P4 significantly improved the severity of VMS at weeks 4 and 12 compared with placebo
  - 0.5 mg E2/50 mg P4 was significant at weeks 7, 9–12



Significantly different from placebo ($P<0.05$) from *Weeks 3–12; †Weeks 7, 9–12; ‡Weeks 6, 7, 9.

Improvement in MENQOL at Week 12

- All TX-001HR doses significantly improved the overall MENQOL and vasomotor MENQOL domain scores from baseline to week 12 compared with placebo
  - Significant improvements were maintained to months 6 and 12, except for 0.25 mg E2/50 mg P4 for the overall score



*P<0.05; †P<0.001 vs placebo.
MENQOL: menopause-specific quality of life questionnaire.

Endometrial Safety

- Endometrial hyperplasia incidence was 0% and no malignancies were detected with any TX-001HR dose or placebo

Treatment, n (%)	Estradiol/Progesterone				Placebo
	1 mg/ 100 mg	0.5 mg/ 100 mg	0.5 mg/ 50 mg	0.25 mg/ 50 mg	
n	280	303	306	274	92
Hyperplasia at 12 months					
Incidence rate	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1-sided upper 95% CI	1.06%	0.98%	0.97%	1.09%	3.20%
Proliferative endometrium					
Screening	2 (0.7)	5 (1.7)	2 (0.7)	1 (0.4)	0 (0)
Month 12	8 (2.9)	5 (1.7)	1 (0.3)	3 (1.1)	0 (0)
Endometrial polyps					
Screening	5 (1.8)	7 (2.3)	5 (1.6)	5 (1.8)	0 (0)
Month 12	4 (1.4)	6 (2.0)	10 (3.3)	7 (2.6)	0 (0)

Safety Endpoints

- All four doses of TX-001HR were well tolerated
- Incidence of TEAEs was low and most TEAEs were mild or moderate in severity
  - Most frequently reported TEAEs (≥5%) were headache, nasopharyngitis, breast tenderness, upper respiratory tract infection, nausea, back pain, abdominal pain
- Serious AEs reported were low and consistent with the age and population studied
  - 7 serious TEAEs were considered related to treatment
- No unexpected safety signals were observed

TEAE: treatment-emergent adverse event.

Conclusions

Significant improvements versus placebo were observed with:

- TX-001HR doses 1.0 mg E2/100 mg P4 or 0.5 mg E2/100 mg P4 in the frequency and severity of moderate-to-severe vasomotor symptoms
  - Met endometrial safety and all 4 co-primary efficacy endpoints
- TX-001HR 0.5 mg E2/50 mg P4 in the frequency of moderate-to-severe vasomotor symptoms by week 6 and severity at most time points from weeks 7 to 12
- TX-001HR 0.25 mg E2/50 mg P4 in the frequency, but not severity, of moderate-to-severe vasomotor symptoms at weeks 4 and 12
- MENQOL scores were improved with all doses at 12 weeks compared to placebo

Conclusions

- TX-001HR was well tolerated with no clinically significant differences in AEs compared with placebo
- The TX-001HR clinical trial provided evidence of endometrial protection
  - See poster LB SUN 07
- TX-001HR, if approved, would be a new oral HT option for postmenopausal women with moderate-to-severe vasomotor symptoms who have an intact uterus
- May be a new option for the estimated millions of women currently using less regulated and unapproved compounded bio-identical HT