REPLENISH Trial: Endometrial Protection with a 17β-Estradiol and Progesterone Combination (TX-001HR) in Menopausal Women with Vasomotor Symptoms

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Disclosures

- Consultant fees: Wyeth/Pfizer, Shionogi Inc., Radius Health Inc., and TherapeuticsMD
- Stock options: TherapeuticsMD

Background

- Hormone therapy (HT) for menopausal women with an intact uterus requires a progestogen to prevent endometrial hyperplasia and reduce the incidence of endometrial cancer[1]
- An estimated 1 to 2.5 million US women use unapproved compounded bio-identical HT (CBHT),[2,3] representing up to 21 to 39 million prescriptions estimated annually[2]
  - Endometrial hyperplasia and endometrial cancer have been reported with CBHT[4-6]
- TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational combination of 17β-estradiol and progesterone (E2/P4; sometimes referred to as bio-identical hormones) in a single oral softgel capsule developed to treat menopausal vasomotor symptoms (VMS) in women with an intact uterus
  - No similar combination HT product has been approved yet in the US or Europe

1. NAMS. *Menopause* 2013;20:888-902. **2.** Pinkerton J, Santoro N. *Menopause* 2015;22:926-936. **3.** Pinkerton J, Constantine G. *Menopause* 2016;23:359-367. **4.** Eden JA, et al. *Med J Aust* 2007;187:244-245. **5**. Davis R, et al. *J Womens Health* (Larchmt) 2014;23:642-648. **6.** Dezman VL, et al. *Int J Gynecol Cancer* 2015;25 Suppl 1:71.

REPLENISH Trial: Objective and Design

Objective: To evaluate the endometrial safety of four doses of TX-001HR in participants of the REPLENISH trial

Design: Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in menopausal 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 menopausal 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 deep vein/artery thrombosis 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 within 2 weeks to 6 months 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

Randomization	Daily 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 daily diaries
  - Frequency and severity of their VMS through week 12
  - Bleeding and spotting through month 12

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

REPLENISH Trial: Safety Study Endpoints

Endpoints		Description
Safety • All women who took ≥1 capsule	Primary	• Incidence of endometrial hyperplasia with up to 12 months of treatment (in women with endometrial biopsies)
	Secondary	• Incidence of AEs and serious AEs • Endometrial bleeding

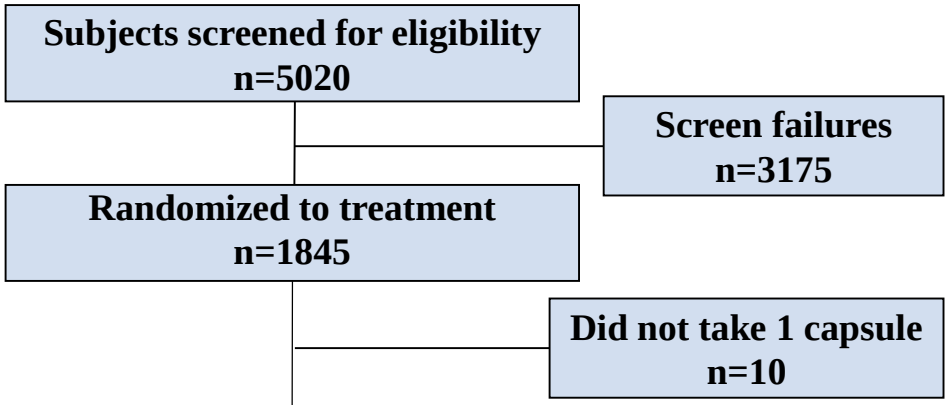
AEs: adverse events.

Statistical Analyses

- 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
  - Incidence of endometrial hyperplasia, per FDA guidance, was planned to be ≤1% with an upper bound of the one-sided 95% CI <4%
  - Biopsies were centrally and sequentially read by 3 independent pathologists
  - Endometrial hyperplasia was diagnosed with a consensus of 2 of 3 pathologists
    - Additional findings such as polyps were also reported
- Endometrial bleeding between treatment groups was analyzed
- AEs and serious AEs were descriptively summarized in all women who took ≥1 capsule (safety population)

Disposition

- 69% of participants completed at 52 weeks



	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
Population, n (%)					
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

- Women had a mean age of 55 years (range, 40 to 66) and a mean BMI of 27 kg/m^2
- 65% of the women were white and 32% 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	415	424	421	424	151
Age, y Mean ± SD	54.7 ± 4.4	54.5 ± 4.5	54.9 ± 4.3	54.4 ± 4.0	54.5 ± 4.3
Race, n (%) White Black Other	 271 (65) 134 (32) 10 (2)	 281 (66) 136 (32) 7 (2)	 276 (66) 133 (32) 12 (3)	 273 (64) 140 (33) 11 (3)	 100 (66) 46 (31) 5 (3)
BMI, kg/m^2 Mean ± SD	26.8 ± 4.1	26.7 ± 4.3	26.7 ± 4.0	26.7 ± 4.0	26.6 ± 3.9

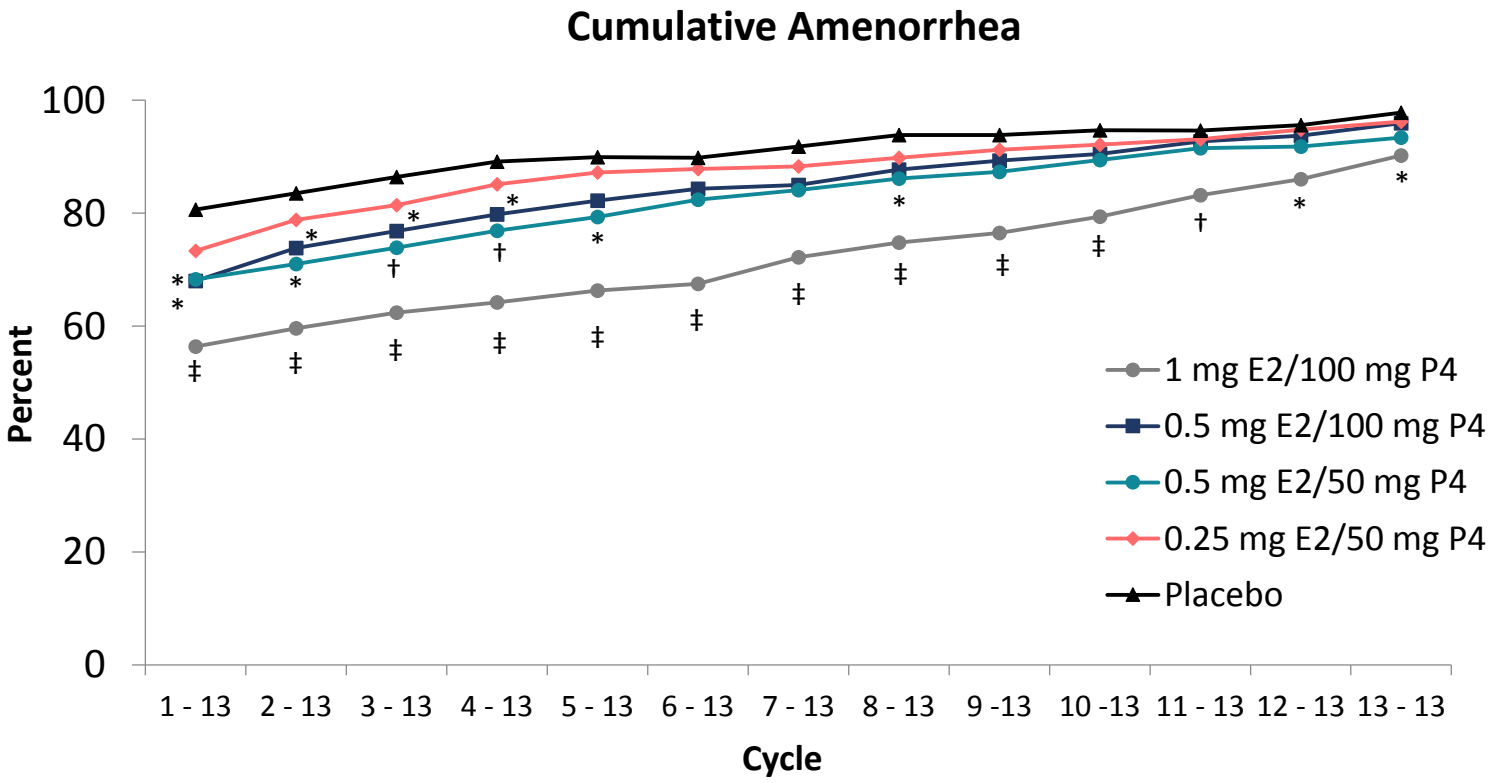
Endometrial Safety

- 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)

Cumulative Amenorrhea

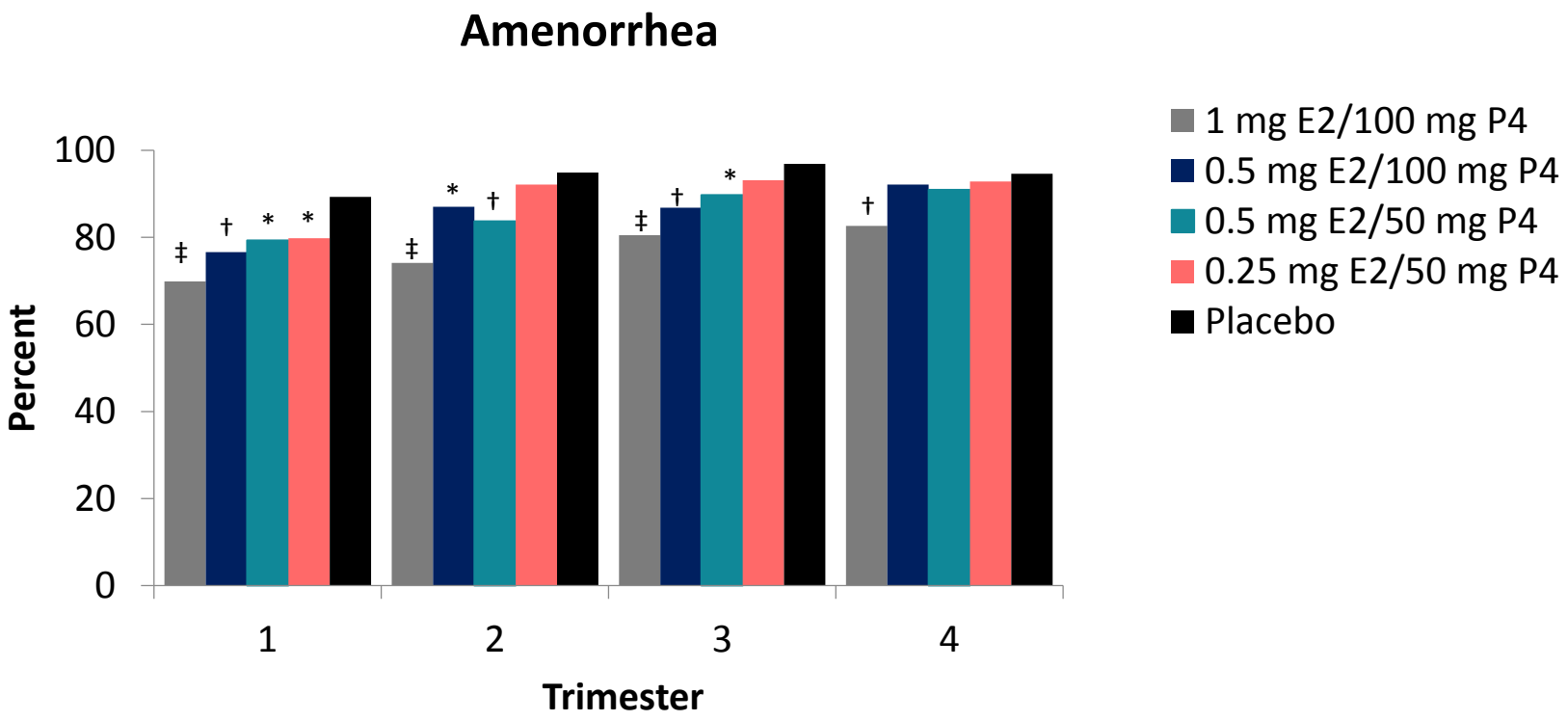
- 56% to 73% of women taking E2/P4 versus 81% taking placebo had amenorrhea from cycle 1 to 13
  - >90% had amenorrhea during cycle 13



*P<0.05; †P<0.01; ‡P<0.001 vs placebo.
Cycles are 28 days in length

Amenorrhea per Trimester

- Percentages of women with amenorrhea
  - 70–80% with TX-001HR vs 89% with placebo during trimester 1
  - Increased to 83–93% with TX-001HR vs 95% with placebo during trimester 4



*P<0.05; †P<0.01; ‡P<0.001 vs placebo.

Safety Endpoints

- 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

- This clinical trial provided evidence of endometrial safety
  - All TX-001HR doses had 0% incidence of endometrial hyperplasia, achieving the ≤1% incidence (1-sided, upper 95% CI <4%) as per FDA guidance
  - No endometrial malignancies were found
- The absence of endometrial hyperplasia and endometrial cancer in this study should be considered in light of case reports of endometrial hyperplasia and endometrial cancer observed with CBHT[1-3]
  - Endometrial safety observed with TX-001HR underscores the need for CBHT safety studies given their potential risks
- If approved, TX-001HR may be an appropriate alternative combination HT with E2/P4 for treating VMS
  - Especially in the estimated millions of menopausal women currently using less regulated and unapproved CBHT

1. Eden JA, et al. *Med J Aust* 2007;187:244-245. **2**. Davis R, et al. *J Womens Health* (Larchmt) 2014;23:642-648. **3.** Dezman VL, et al. *Int J Gynecol Cancer* 2015;25 Suppl 1:71.