REPLENISH trial: TX-001HR (17β-Estradiol and Progesterone Combination) Significantly Improved Moderate to Severe Hot Flushes in Menopausal Women

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Disclosures

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

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 CBHT,[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 in a single table/capsule 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 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

- Menopausal 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

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)
	Secondary	• Incidence of AEs and serious AEs

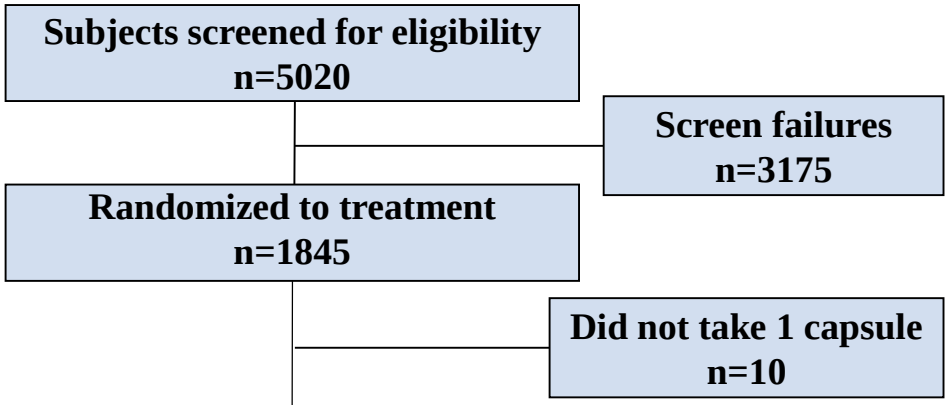
AEs: adverse events; VMS: vasomotor symptoms.

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



	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 (%)					
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) 45 (32) 1 (1)	 99 (66) 48 (32) 2 (1)	 99 (67) 43 (29) 5 (3)	 102 (66) 48 (31) 4 (3)	 91 (67) 41 (30) 3 (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

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)

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

Conclusions

- The TX-001HR clinical trial provided evidence of endometrial protection
- TX-001HR, if approved, would be a new oral HT option for menopausal 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