17β-Estradiol/Progesterone in a Single Oral Softgel Capsule (TX-001HR) Significantly Reduced Moderate-to-Severe Vasomotor Symptoms without Endometrial Hyperplasia

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Disclosures

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Background

- Use of compounded bioidentical hormone therapy (CBHT) 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] representing up to 21 to 39 million prescriptions annually[1,2]
  - Some compounded products may be associated with increased risks[3]
    - Reports[4-7] and a NAMS survey (n=1064)[8] suggest an increase in uterine bleeding and endometrial hyperplasia/cancer with CBHT
  - CBHT products are not FDA-approved[9] and NAMS/ACOG/ENDO societies[10-12] recommend against the use of CBHT
- No HT formulation combining 17β-estradiol and progesterone is FDA approved
- TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational combination of 17β-estradiol and progesterone (sometimes referred to as bioidentical hormones) in a single, oral, softgel capsule

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. **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. **7.** Gersak K et al. *Climacteric* 2014;17(Suppl 1):58-59. **8.** Gass M et al. *Menopause* 2015:22;1276-1284. **9.** Compounding and the FDA. Questions and Answers. Available at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm339764.htm. Accessed on 3 Oct 2017. **10.** NAMS. *Menopause.* 2017;24:728-753. **11.** ACOG. *Obstet Gynecol.* 2014;123:202-216. **12.** Stuenkel CA, et al. *J Clin Endocrinol Metab.* 2015;100:3975-4011.

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 (VMS)
- **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 VMS

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>VMS Substudy</u>

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

Key Exclusion Criteria

- History of hyperplasia or neoplasia of hormone dependent tissues
- History of thrombosis of deep veins/arteries
- Abnormalities of the gastrointestinal system
- Abnormal function of other hormone producing glands
- Prior use of estrogen-, progestogen-, androgen-, SERM products
- Medications known to induce or affect estrogen and/or progestogen drug metabolism or activity

Study Design: Randomization

VMS substudy

- ≥7/day or ≥50/week moderate-to-severe hot flushes
- Randomized 1:1:1:1:1

Treatment Groups

- 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

General study

- Did not qualify for VMS substudy
- Randomized 1:1:1:1

- TX-001HR was taken daily for 12 months (VMS substudy was 12 weeks)
- Both populations were assessed for general and endometrial safety
- All women completed a daily diary on the frequency and severity of their VMS through week 12

REPLENISH Trial: Study Endpoints

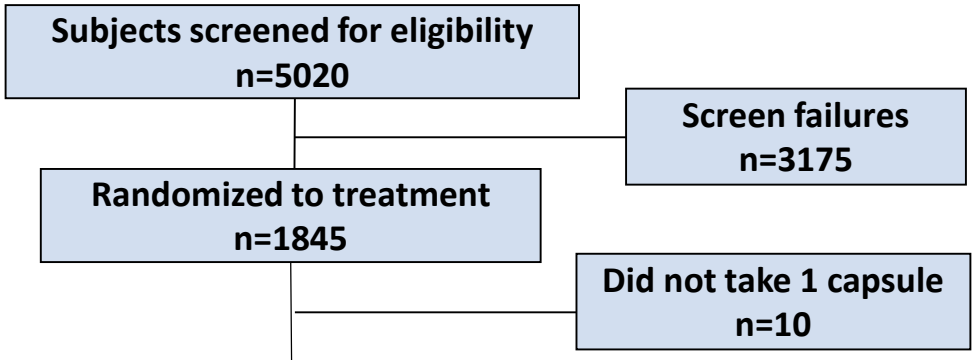
Endpoints		Description
Efficacy • VMS substudy	**4 co-primary endpoints**	**VMS frequency (moderate-to-severe)** • Mean change from baseline to week 4 • Mean change from baseline to week 12 **VMS severity** • Mean change from baseline to week 4 • Mean change from baseline to week 12
	Secondary	• Mean 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 adverse events (AEs) and serious AEs

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.

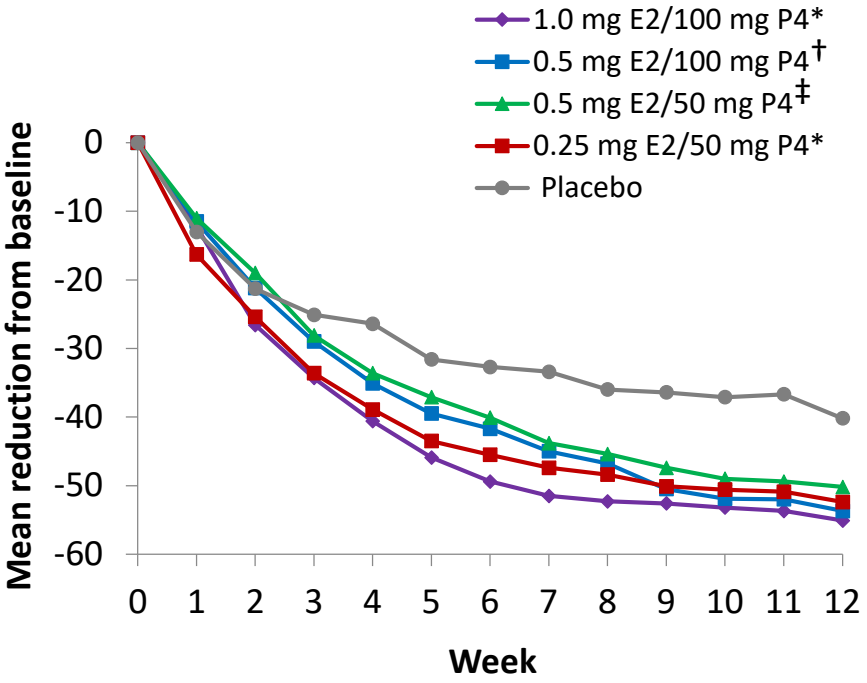
Demographics of VMS Substudy

- Mean age: 55 years (range, 40 to 65) and mean BMI: 27 kg/m^2
- 67% of the women were white and 31% were 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 (2.6)	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 significant and clinically meaningful[1] reductions in the weekly frequency of moderate-to-severe VMS from baseline at weeks 4 and 12 versus placebo
  - Except for 0.5 mg E2/50 mg P4, which reached significance at week 6
- Mean daily number of moderate-to-severe VMS decreased from 10–11/day at baseline to 2–4/day with TX-001HR (5/day for placebo) at week 12

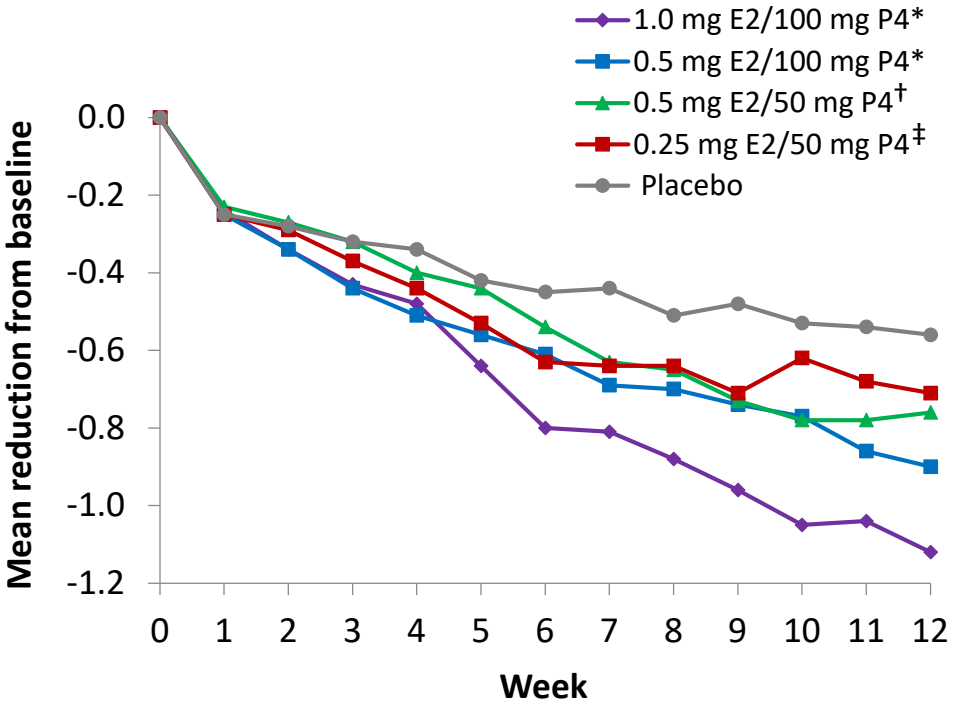


P<0.05 from *Weeks 3–12; †Weeks 4–12; ‡Weeks 6-12 vs placebo.

[1]Data presented in the Top Scoring Abstract Session: Constantine G, et al. TX-001HR is associated with a clinically meaningful effect on vasomotor symptoms.

Weekly Improvement in VMS Severity

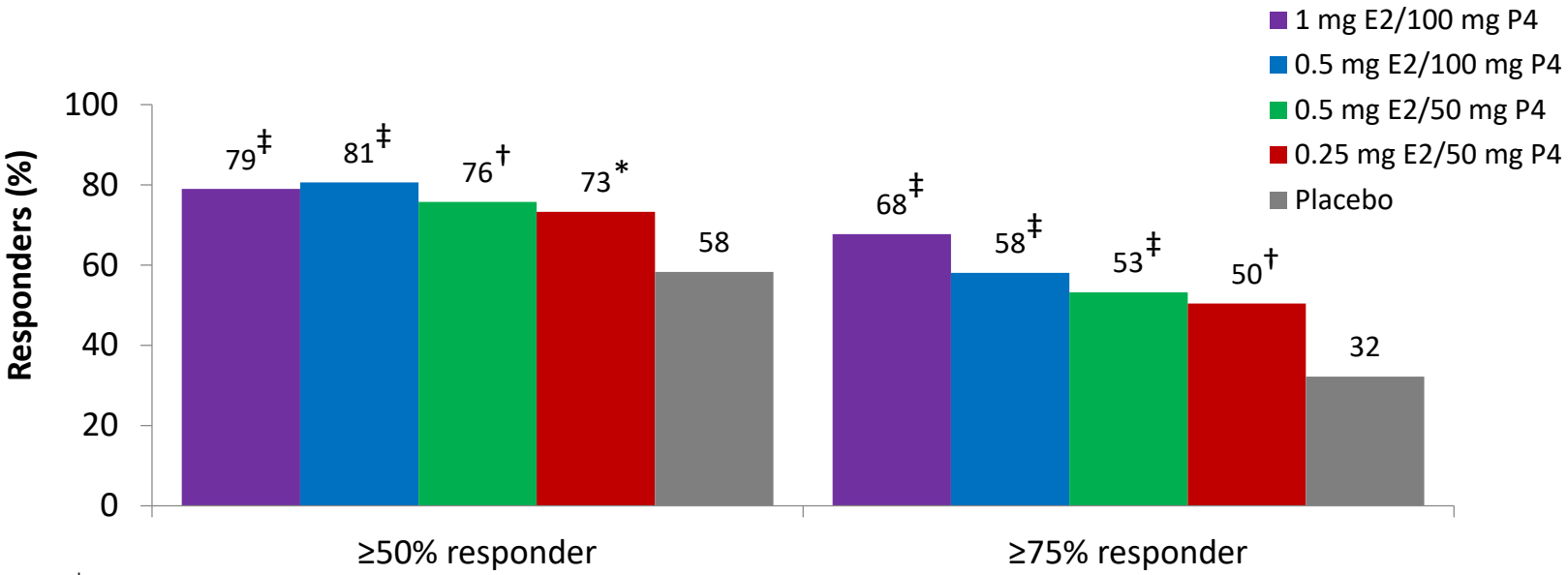
- Doses 1.0 mg E2/100 mg P4 and 0.5 mg E2/100 mg P4 significantly improved the severity of VMS at weeks 4 and 12 compared with placebo
  - 0.5 mg E2/50 mg P4 was significant at weeks 7, 9–12
  - 0.25 mg E2/50 mg P4 was significant at weeks 6, 7 and 9



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

Responder Analysis

- Significantly more women had ≥50% or ≥75% reduction in their moderate-to-severe VMS frequency with TX-001HR than with placebo at 12 weeks



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

Responders defined as ≥50% or ≥75% reduction in frequency of moderate-to-severe VMS from baseline to week 12.

Endometrial Safety

- Endometrial hyperplasia incidence was 0%
- No endometrial malignancies detected with any TX-001HR dose or placebo at 12 months

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)

*Includes proliferative endometrium and disordered proliferative endometrium.

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
- Minimal clinically meaningful changes in lipid, coagulation and glucose parameters
- No unexpected safety signals were observed

TEAE: treatment-emergent adverse event.

Conclusions

Significant and clinically meaningful 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 VMS at weeks 4 and 12
- TX-001HR 0.5 mg E2/50 mg P4 in the frequency of moderate-to-severe VMS 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 VMS at weeks 4 and 12

Conclusions

- This TX-001HR clinical trial provided evidence of endometrial protection
- TX-001HR, if approved, would represent a new oral HT option for menopausal women with moderate-to-severe VMS who have an intact uterus
  - TX-001HR may be a new option for the estimated millions of women currently using unapproved compounded BHT, which is associated with safety concerns