Effects of TX-001HR on Uterine Bleeding Rates in Menopausal Women with Vasomotor Symptoms

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Disclosures

- **Advisory board:** Abbvie, Allergan, IBSA, Pfizer, and TherapeuticsMD
- **Consultant:** Cook ObGyn and Cooper Surgical

Uterine Bleeding with VMS Treatments

- Use of compounded bioidentical HT (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]
- Uterine bleeding can be associated with endometrial pathology
  - Reports[3-6] and a NAMS survey (n=1064)[7] suggest an increase in uterine bleeding and endometrial hyperplasia/cancer with CBHT
- Compared with progestins, progesterone was shown to have less impact on the angiogenic/antiangiogenic balance in the endometrium[8]
- No HT product combining 17β-estradiol and progesterone is FDA approved

HT: hormone therapy; NAMS: North American Menopause Society; VMS: vasomotor symptoms

1. Pinkerton J and Santoro N. *Menopause* 2015;22:926-936. **2.** Pinkerton J and Constantine G. *Menopause* 2016;23:359-367. **3.** Eden JA et al. *Med J Aust* 2007;187:244-245. **4.** Davis R et al. *J Womens Health (Larchmt)* 2014;23:642-648. **5.** Dezman VL et al. *Int J Gynecol Cancer* 2015;25 Suppl 1:71. **6.** Gersak K et al. Climacteric 2014;17(Suppl 1):58-59. **7.** Gass M et al. *Menopause* 2015:22;1276-1284. 8. Archer DF. *Menopause.* 2011;18:416-420.

REPLENISH Trial

- **Endpoints:** To evaluate endometrial safety (primary) and uterine bleeding (secondary) of four daily TX-001HR (E2/P4) doses versus placebo given in the REPLENISH trial to treat moderate-to-severe vasomotor symptoms
  - TX-001HR (TherapeuticsMD, Boca Raton, FL) is an investigational combination of 17β-estradiol and progesterone in a single, oral, softgel capsule
- **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
  - 12-week efficacy substudy for the treatment of vasomotor symptoms

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

- 1.0 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

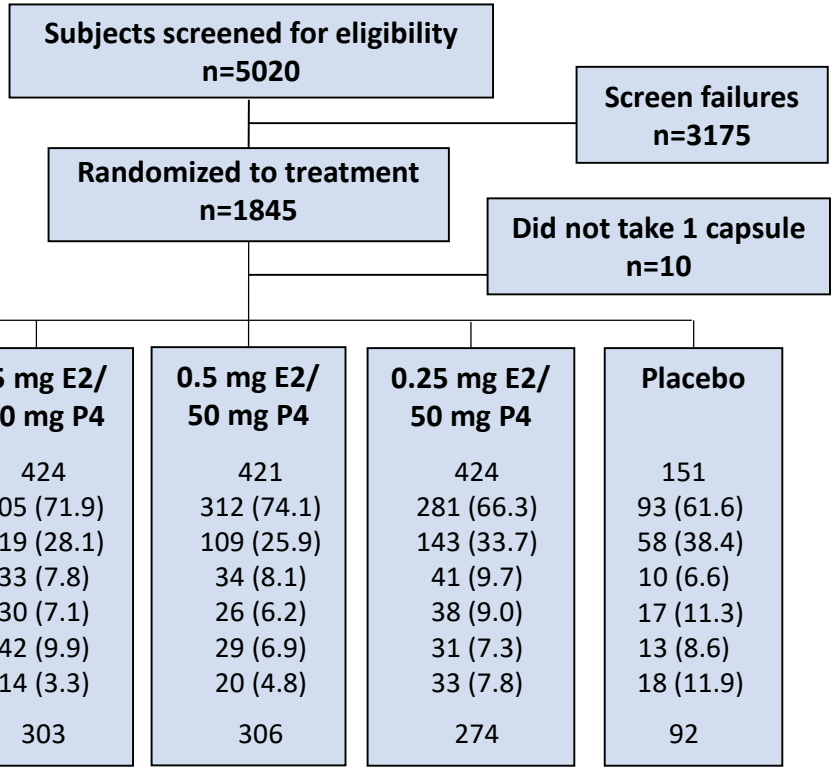
General study (12 mos)

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

- Both populations were assessed for general and endometrial safety
- Endometrial bleeding profiles, including cumulative amenorrhea (no bleeding or spotting) were assessed over thirteen 28-day cycles between treatment groups
  - All women completed diaries of daily bleeding (requiring sanitary protection) and spotting (not requiring sanitary protection) up to month 12

Disposition and Demographics

- 69% of women completed at 52 weeks
- Mean age: 55 years (40–66)
- Mean BMI: 27 kg/m^2
- 65% were white and 32% black

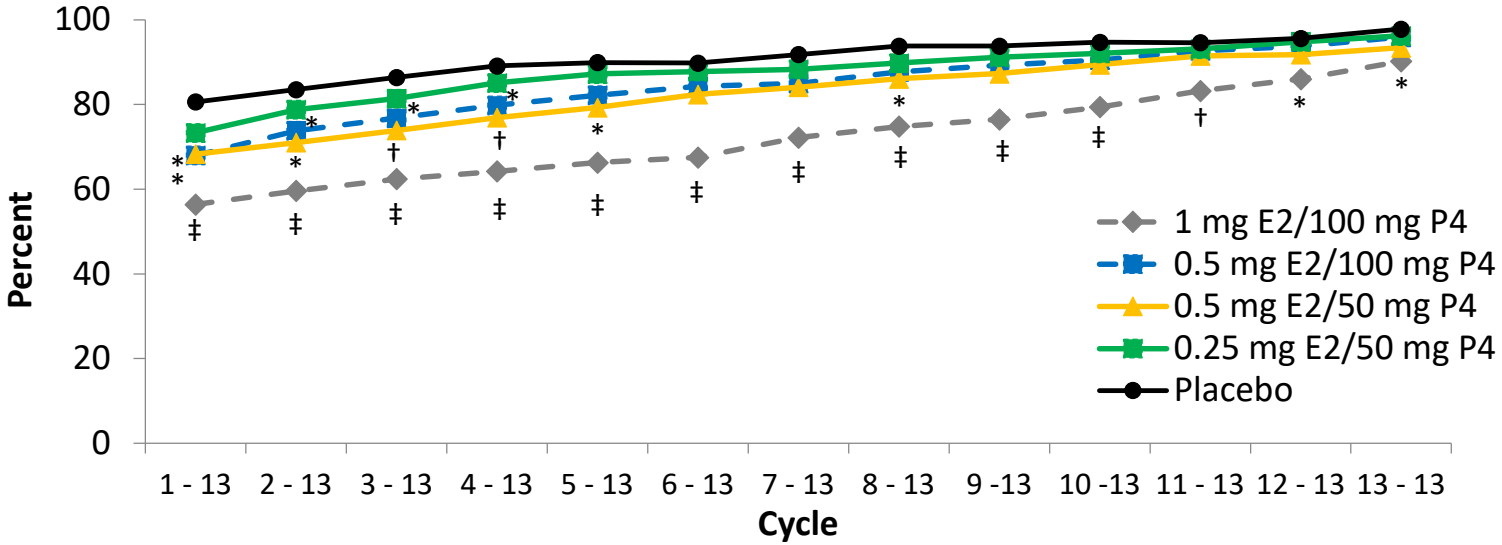


	1.0 mg E2/ 100 mg P4	0.5 mg E2/ 100 mg P4	0.5 mg E2/ 50 mg P4	0.25 mg E2/ 50 mg P4	Placebo
Population, n (%)					
Safety	415	424	421	424	151
Completed at 52 weeks	284 (68.4)	305 (71.9)	312 (74.1)	281 (66.3)	93 (61.6)
Discontinued	131 (31.6)	119 (28.1)	109 (25.9)	143 (33.7)	58 (38.4)
Adverse event	46 (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.

Cumulative Amenorrhea

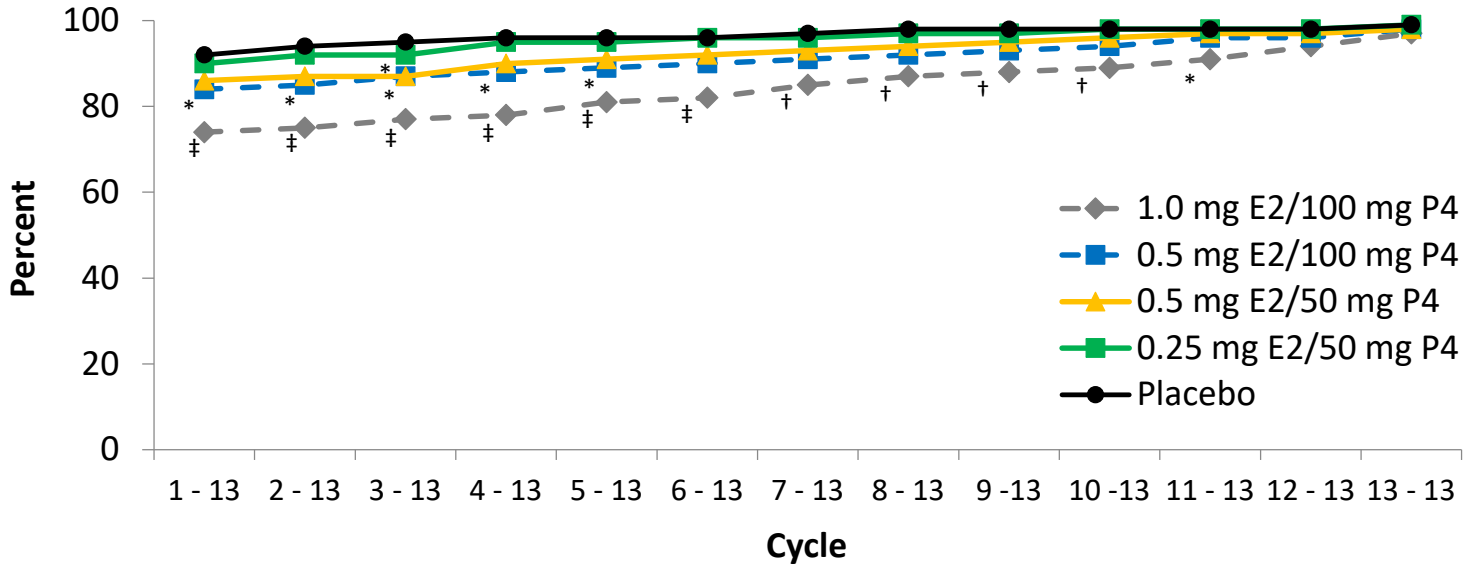
- Cumulative amenorrhea from cycle 1 to 13 was high with TX-001HR (56–73%), but lower than with placebo (81%), and increased over time
  - >90% had amenorrhea during cycle 13



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

Cumulative No Bleeding

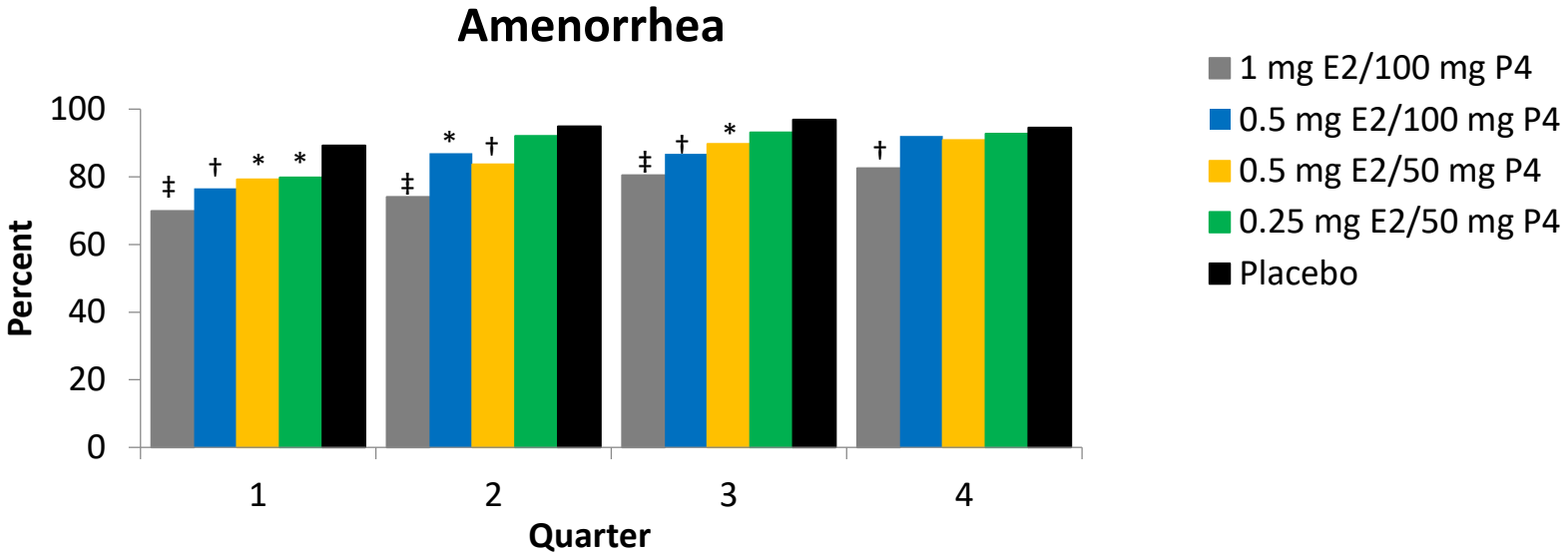
- Women with no bleeding was high (74–90%) with TX-001HR



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

Amenorrhea per Quarter

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



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

Endometrial Safety

- Endometrial hyperplasia incidence was 0%
- No endometrial malignancies 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)

*Includes proliferative endometrium and disordered proliferative endometrium.

Adverse Events Related to Vaginal Bleeding

- Few vaginal bleeding adverse events were reported

Vaginal bleeding TEAEs, n (%)	Estradiol/Progesterone				Placebo (n=151)
	1 mg/100 mg (n=415)	0.5 mg/100 mg (n=424)	0.5 mg/50 mg (n=421)	0.25 mg/50 mg (n=424)	
Postmenopausal hemorrhage	2 (0.5)	0	0	0	0
Uterine hemorrhage	3 (0.7)	1 (0.2)	1 (0.2)	0	0
Vaginal hemorrhage	14 (3.4)	10 (2.4)	3 (0.7)	8 (1.9)	1 (0.7)

- Discontinuation due to bleeding was low
  - TX-001HR: 0.5–1.45%
  - Placebo: 0%

TEAE: treatment-emergent adverse event.

Cumulative Amenorrhea Rates with HT

- Based upon prescribing information or clinical data; not head-to-head comparison

Products	Doses	Cumulative Amenorrhea (%)
		Cycle 1 to Cycle 13
Prempro® (CEE/MPA)[1]	0.625 mg / 5 mg 0.625 mg / 2.5 mg 0.45 mg / 1.5 mg 0.3 mg / 1.5 mg	26 23 42 45
Activella® (E2/NETA)[2]	1.0 mg / 0.5 mg	49
Angeliq® (E2/DRSP)[3]	1.0 mg / 0.5 mg	45
TX-001HR (E2/P4)	1.0 mg / 100 mg 0.5 mg / 100 mg 0.5 mg / 50 mg 0.25 mg / 50 mg	56 68 68 73
Placebo		81

CEE: conjugated equine estrogens; DRSP: drospirenone; MPA: medroxyprogesterone acetate; NETA: norethisterone acetate.

1. Prempro® tablets prescribing information. Wyeth Pharmaceuticals. **2.** Activella® tablets prescribing information. Novo Nordisk FemCare AG. **3.** Angeliq® Tablets prescribing information. Berlex.

Conclusions

- Amenorrhea rates were high in users of TX-001HR
- This clinical trial provided evidence of endometrial safety with TX-001HR at 12 months
  - Absence of endometrial hyperplasia and cancer here should be considered in light of case reports of endometrial hyperplasia and cancer observed with compounded bioidentical HT use*[1-4]
  - Endometrial safety observed with TX-001HR underscores the need for compounded bioidentical HT safety studies given their potential risks
- If approved, TX-001HR may be an appropriate alternative combination HT with E2/P4 for treating moderate-to-severe VMS
  - Especially in the estimated millions of menopausal women currently using less regulated and unapproved compounded bioidentical HT

*Compounded bioidentical HT use ranged from unknown to several years; most were ~2 years.

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. **4.** Gersak K et al. Climacteric 2014;17(Suppl 1):58-59.