Menopause: *Original Research*

A 17β-Estradiol–Progesterone Oral Capsule for Vasomotor Symptoms in Postmenopausal Women

A Randomized Controlled Trial

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OBJECTIVE: To evaluate efficacy, endometrial safety, and overall safety of a single-capsule 17β-estradiol–progesterone (TX-001HR) for treating menopausal moderate-to-severe vasomotor symptoms.

METHODS: REPLENISH was a phase 3, 12-month, randomized, double-blind, placebo-controlled, multicenter trial. Women (aged 40–65 years) with vasomotor symptoms and a uterus were randomized to daily estradiol (mg)–progesterone (mg) (1/100, 0.5/100, 0.5/50, or 0.25/50), and women in the vasomotor symptoms substudy (women with moderate-to-severe hot flushes [seven or greater per day or 50 or greater per week]) to those estradiol–progesterone doses or placebo. The primary safety endpoint was endometrial hyperplasia incidence at 12 months in all women (the total population), and the primary efficacy endpoints were frequency and severity changes (from daily diaries) in moderate-to-severe vasomotor symptoms with estradiol–progesterone compared with placebo at weeks 4 and 12 in the vasomotor symptoms substudy. A sample size of 250 women in each active treatment arm with two or less endometrial hyperplasia cases would result in 1% or less

annual incidence (upper bound 2.5% or less, one-sided 95% CI).

RESULTS: One thousand eight hundred forty-five women were enrolled and randomized from August 2013 to October 2015; 1,835 received medication (safety population); 1,255 were eligible for the endometrial safety population; 726 comprised the vasomotor symptoms substudy; their mean age and body mass index were 55 years and 27, respectively; one third were African American. No endometrial hyperplasia was found. Frequency and severity of vasomotor symptoms significantly decreased from baseline with 1 mg estradiol and 100 mg progesterone and 0.5 mg estradiol and 100 mg progesterone compared with placebo at week 4 (frequency: by 40.6 and 35.1 points [1 mg and 100 mg and 0.5 mg and 100 mg, respectively] vs 26.4 points [placebo]; severity: by 0.48 and 0.51 vs 0.34 points) and week 12 (by 55.1 and 53.7 vs 40.2; severity: by 1.12 and 0.90 vs 0.56); 0.5 mg estradiol and 50 mg progesterone improved ($P<.05$) frequency and severity at week 12, and 0.25 mg estradiol and 50 mg progesterone frequency but not severity at weeks 4 and 12.

CONCLUSION: No endometrial hyperplasia was observed while single-capsule estradiol–progesterone provided clinically meaningfully improvements in moderate-to-severe vasomotor symptoms. This estradiol–progesterone formulation may represent a new option, using naturally occurring hormones, for the estimated millions of women using nonregulatory-approved, compounded hormone therapy.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT01942668.

Use of unapproved, compounded hormone therapy (HT) is of epidemic proportions in the United States; recent annual estimates were 1–2.5 million U.S. women taking 21–39 million prescriptions.[1] Many women stopped taking U.S. Food and Drug Administration (FDA)–approved HT[2] in favor of non–FDA-approved, compounded HT after the first publication[3] of Women's Health Initiative findings.[4–7] Compounded HT has not been rigorously tested for efficacy and safety and may be associated with risks women may not be aware of,[8] including insufficient endometrial protection resulting in endometrial cancer or hyperplasia (Dezman VL, Gersak MZ, Gersak K. Two case of atypical endometrial hyperplasia associated with 'bioidentical' hormone replacement therapy: IGCS-0084 uterine cancer, including sarcoma [abstract]. Int J Gynecol Cancer 2015;25(suppl 1):71.).[9,10] Nonetheless, many women take compounded "natural" products, falsely believing they are safer options.[6,7,11]

Recent reports suggest a potentially safer profile of micronized progesterone compared with synthetic progestogens for breast cancer[12,13] and venous thromboembolism.[14] However, because natural progesterone is approved by the FDA for endometrial protection only at 200 mg cyclically in women using 0.625 mg of conjugated equine estrogens, the many clinicians prescribing progesterone continuously or with other estrogens do so in the absence of rigorous evidence confirming endometrial protection. Noteworthy is the fact that dose, duration, and ratio of estrogens to progesterone can affect endometrial protection.

No formulation combining natural 17β-estradiol and progesterone (both molecularly and chemically identical to endogenous hormones) has been approved by the FDA to treat moderate to severe vasomotor symptoms. The REPLENISH trial evaluated the efficacy and safety of four daily estradiol–progesterone doses in a single, oral, softgel capsule (TX-001HR).

MATERIALS AND METHODS

The REPLENISH trial (NCT01942668) was a phase 3, prospective, randomized, double-blind, placebo-controlled, multicenter trial conducted at 117 U.S. sites. Enrollment occurred from August 2013 to October 2015. The study was conducted in accordance with Good Clinical Practice guidelines of the FDA. The protocol and its amendments, participant consent form, and recruitment materials were approved by one of the following central or local institutional review boards: Schulman Associates institutional review board, Inc, Cincinnati, Ohio; Chesapeake institutional review board, Columbia, Maryland; Columbia University Medical Center institutional review board, New York, New York; Western institutional review board, Puyallup, Washington; University of Virginia institutional review board for Health Science Research, Charlottesville, Virginia; and Crescent City institutional review board, New Orleans, Louisiana.

Healthy menopausal women (40–65 years; body mass index [BMI, calculated as weight (kg)/[height (m)]^2] 34 or less) with an intact uterus seeking vasomotor symptom treatment were eligible. Women were considered "menopausal" with 12 months or greater of spontaneous amenorrhea; at least 6 months of spontaneous amenorrhea with a screening serum follicle-stimulating hormone greater than 40 milli-international units per milliliter; or 6 weeks or greater after bilateral oophorectomy. All participants provided written informed consent.

Key exclusion criteria were contraindications or allergy to estrogens, progestins, or progesterone; a history of thromboembolic disorder, coronary artery or cerebrovascular disease, clotting disorder, estrogen-dependent neoplasia, chronic kidney or liver disease, diabetes, or other endocrine disease; a history of melanoma, or breast, uterine, or ovarian cancer; a history of endometrial hyperplasia or undiagnosed vaginal bleeding; uterine fibroids diagnosed at screening; heavy smoking (15 cigarettes per day or greater), or a history of drug or alcohol abuse.

Women could not have used any estrogen pellets or progestational injected drugs (within 6 months); intrauterine device (within 12 weeks); oral, transdermal, or vaginal estrogen (alone or with progestin), selective estrogen receptor modulator or androgen-containing preparation (within 8 weeks), medication known to be a CYP3A4 enzyme inducer or inhibitor (within 4 weeks); or medication (including over-the-counter) that could alter estrogen or progesterone activity or vasomotor symptoms (within 4 weeks). During the study, women could not use any estrogen, progestin, progesterone, or selective estrogen receptor modulator other than study medications; any CYP3A4 inducers or inhibitors; or any medications (including herbal or nutritional preparations) that could affect the vasomotor symptom study endpoints.

Randomization was performed by the clinical research organization using a reproducible, computer-generated, block schedule with a block size of five for the vasomotor symptoms substudy and four for the nonsubstudy. All investigators, involved staff, and participants were blinded using a double-dummy technique because different doses were different-sized capsules.

Enrolled participants were randomized 1:1:1:1 to the four active, daily, oral estradiol–progesterone doses of TX-001HR (estradiol/progesterone at 1 mg and 100 mg, 0.5 mg and 100 mg, 0.5 mg and 50 mg, or 0.25 mg and 50 mg) for 12 months for inclusion in the safety population and potentially the endometrial safety population. If women had moderate-to-severe vasomotor symptoms (seven or greater per day or 50 or greater per week) at enrollment, they were instead randomized 1:1:1:1:1 to the estradiol–progesterone doses or placebo for 12 months to be included in the vasomotor symptoms substudy, but were also considered for eligibility in the safety and endometrial safety populations. The safety population included all randomized women from either randomization scheme who took at least one dose of medication; this population was used for the overall safety analysis. The endometrial safety population included all women randomized to active treatment (from either randomization scheme) who completed 12 treatment months and had evaluable baseline and 12-month biopsies; this population was used for the primary safety endpoint analysis of endometrial safety. The modified intent-to-treat vasomotor symptoms VMS population included all treated participants from the vasomotor symptoms substudy who had measurements of frequency and severity of hot flush data at baseline and at least 1 week during treatment; this population was used for the primary efficacy endpoint analysis. Although the efficacy analysis was 12 weeks, women in the vasomotor symptoms study continued taking medication for 12 months for their potential inclusion in the endometrial safety population.

The primary safety endpoint was the incidence of endometrial hyperplasia with estradiol–progesterone at 12 months (in the endometrial safety population). Endometrial biopsies were taken to assess endometrial hyperplasia at screening and at 12 months (treatment end) or study discontinuation at 12 weeks or greater. Biopsies were processed centrally, read by three pathologists, and categorized as 1=no endometrial hyperplasia or malignancy (proliferative or secretory endometrium; insufficient tissue for diagnosis); category 2=endometrial hyperplasia (simple or complex hyperplasia with or without atypia); or category 3=endometrial malignancy. The majority among two of the three pathologists determined the final diagnosis; reading of the third pathologist was used when disagreement occurred. A secondary safety endpoint included the proportion of women with cumulative amenorrhea (absence of bleeding [requiring sanitary protection] or spotting [not requiring sanitary protection]) over 12 months. All women completed daily bleeding diaries up to 12 months.

The secondary safety endpoint of adverse events (occurring any time after first study dose) and treatment-emergent adverse events (occurring on or after the first study dose through 15 days after the last study dose) were summarized by preferred terms using the Medical Dictionary for Regulatory Activities in the safety populations. Adverse events were evaluated at each visit and assessed for seriousness, severity, duration, outcomes, and treatment relationship. A woman who experienced more than one of the same treatment-emergent adverse events was counted once for that treatment-emergent adverse event; if a woman had the same treatment-emergent adverse event more than once, the event with the worst severity and strongest treatment relationship was counted. Serious adverse events (life-threatening,

requiring hospitalization, or jeopardizing the patient and requiring medical or surgical intervention) were collected through 30 days after the last study dose. Lipid, coagulation, and chemistry parameters were collected at baseline, week 12, and months 6, 9, and 12 and were summarized descriptively.

The primary efficacy analysis included four coprimary efficacy endpoints of mean changes in frequency and severity of moderate-to-severe vasomotor symptoms from baseline to weeks 4 and 12 with active treatments compared with placebo in the modified intent-to-treat vasomotor symptoms population. Women completed daily diaries for hot flush frequency and severity up to week 12. Weekly hot flush frequency was the total number of moderate and severe hot flushes in the previous 7 days. Hot flush severity was defined as mild (sensation of heat without sweating), moderate (sensation of heat with sweating but able to continue activities), or severe (sensation of heat, sweating, and need to stop activities). The weekly hot flush severity score was calculated as: ([number of mild hot flushes over 7 days×1]+[number of moderate hot flushes over 7 days×2]+[number of severe hot flushes over 7 days×3])÷(total number of hot flushes over 7 days). Secondary efficacy outcomes included mean changes from baseline in frequency and severity of moderate-to-severe vasomotor symptoms at each week up to week 12 and in the Clinical Global Impression at weeks 4, 8, and 12 (used to determine clinical meaningful thresholds for vasomotor symptom reductions).

With a sample size (based on a 12-month endometrial hyperplasia incidence of 1% or less with an upper 95% CI bound of 4% or less) of 250 women in each active treatment arm completing 12 months of treatment (with a readable end-of-study biopsy), two or less cases of endometrial hyperplasia would result in an annual incidence of 1% or less with an upper bound of the one-sided 95% CI of 2.5% or less. The vasomotor symptoms substudy sample size of 150 women per group would provide 90% power to test the primary endpoints (allowing for 20% of participants to discontinue) based on a mean reduction in weekly frequency of moderate-to-severe hot flushes of 56 or greater from baseline with any active treatment (35 with placebo) and in severity of any hot flushes of 0.7 or greater from baseline with any active treatment (0.4 with placebo) at weeks 4 and 12.

Changes in frequency and severity of vasomotor symptoms for the four coprimary endpoints and secondary endpoints were analyzed using a mixed model for repeated-measures analysis with baseline as a covariate and treatment, study week, and treatment-by-study week interaction as fixed factors. Each combined estradiol–progesterone dose was compared with placebo for the four coprimary endpoints and secondary efficacy parameters using a gatekeeping approach to account for multiple comparisons. The highest combined dose (1 mg estradiol and 100 mg progesterone) was compared with placebo first; if statistical significance was reached for all coprimary endpoints, the next lower dose (0.5 mg estradiol and 100 mg progesterone) was analyzed; this procedure was subsequently followed for the next consecutively lower doses. Missing or invalid data were not imputed (as per mixed model for the repeated-measures method).

Results were statistically significant at $P<.05$. An endometrial hyperplasia incidence rate of 1% or less with an upper limit of the one-sided 95% CI of 4% or less was considered acceptably low as per the FDA.[15]

RESULTS

Of 1,845 randomized women, 1,835 received one or more capsules and were included in the safety population, of whom 1,275 completed 52 weeks (Fig. 1). Demographics of the safety population are shown in Table 1. Of the 1,835 women in the safety population 1,255 were eligible for the endometrial safety population.

Of the 726 women eligible for the modified intent-to-treat vasomotor symptoms population (efficacy analysis), 647 (89%) completed the 12-week substudy. Discontinuation as a result of lack of efficacy was 0–1.9% with estradiol–progesterone vs 8.9% with placebo over 52 weeks. Women in the modified intent-to-treat vasomotor symptoms population had a mean age of 55 years, mean BMI of 27, and mean time since menopause of 5.9 years; one third were African American; these demographics were similar to those of the safety population (Table 1). At baseline, mean weekly number of moderate-to-severe vasomotor symptoms ranged from 72.1 to 77.0, and mean weekly severity scores ranged from 2.50 to 2.54 in the vasomotor symptoms substudy.

No cases of endometrial hyperplasia were observed with any estradiol–progesterone dose (0% incidence; primary safety endpoint; Table 2). No endometrial cancer and low incidence of endometrial proliferation (2.9% or less) and endometrial polyps (3.3% or less) were found (Table 2). Cumulative amenorrhea rates with estradiol–progesterone increased over time (Fig. 2). Amenorrhea rates were similar among groups (except for 1 mg estradiol and 100 mg progesterone vs placebo; $P=.023$) by cycle 13
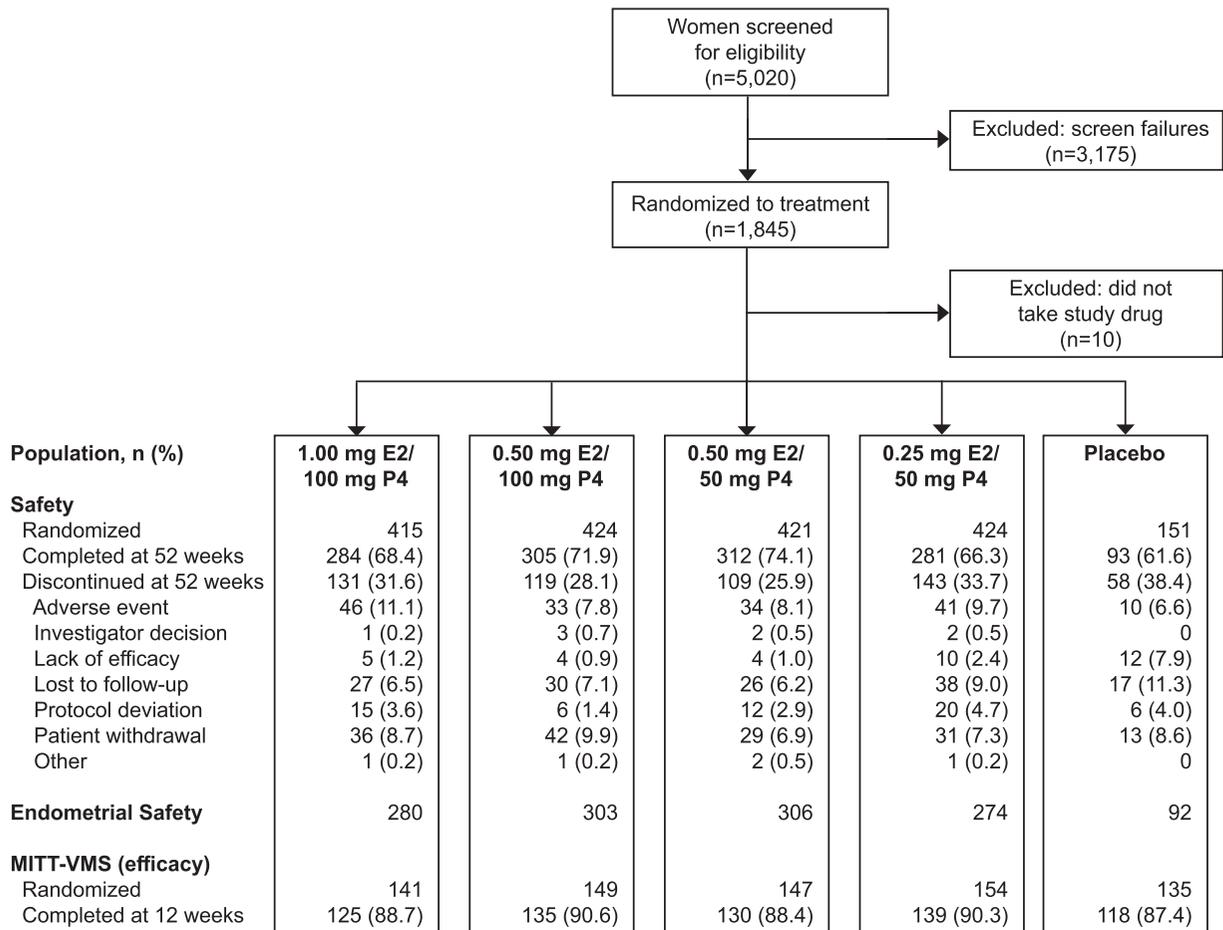
Women screened
for eligibility
(n=5,020)

Excluded: screen failures
(n=3,175)

Randomized to treatment
(n=1,845)

Excluded: did not
take study drug
(n=10)

Population, n (%)	1.00 mg E2/ 100 mg P4	0.50 mg E2/ 100 mg P4	0.50 mg E2/ 50 mg P4	0.25 mg E2/ 50 mg P4	Placebo
Safety					
Randomized	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 at 52 weeks	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)
Investigator decision	1 (0.2)	3 (0.7)	2 (0.5)	2 (0.5)	0
Lack of efficacy	5 (1.2)	4 (0.9)	4 (1.0)	10 (2.4)	12 (7.9)
Lost to follow-up	27 (6.5)	30 (7.1)	26 (6.2)	38 (9.0)	17 (11.3)
Protocol deviation	15 (3.6)	6 (1.4)	12 (2.9)	20 (4.7)	6 (4.0)
Patient withdrawal	36 (8.7)	42 (9.9)	29 (6.9)	31 (7.3)	13 (8.6)
Other	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.2)	0
Endometrial Safety	280	303	306	274	92
MITT-VMS (efficacy)					
Randomized	141	149	147	154	135
Completed at 12 weeks	125 (88.7)	135 (90.6)	130 (88.4)	139 (90.3)	118 (87.4)

Fig. 1. Participant disposition. MITT-VMS, modified intent-to-treat vasomotor symptoms.

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(range 90.2% [highest dose] to 96.2% [lowest dose] vs 97.8% [placebo]).

The incidence of treatment-emergent adverse events was low in all treatment groups (Table 3); differences in treatment-emergent adverse events with estradiol–progesterone compared with placebo were not clinically important. Most treatment-emergent adverse events were mild or moderate in severity. The most common treatment-related, treatment-emergent adverse events (3% or greater of women) with an incidence numerically higher for estradiol–progesterone (at any dose) than with placebo were breast tenderness, headache, nausea, pelvic pain, vaginal bleeding, and vaginal discharge. Adverse events leading to discontinuation occurred in 7.3–11% with estradiol–progesterone vs 6.6% with placebo (Table 3).

Forty participants reported 47 treatment-emergent serious adverse events; those considered treatment-related did not occur with any dose depen-

dence and included acute pancreatitis, deep vein thrombosis (woman with prior left femoral popliteal bypass surgery and a family history of deep vein thrombosis), chronic obstructive pulmonary disease, infective cholecystitis, and breast cancer (Table 3). One death not considered related to treatment (metastatic, nonsmall cell lung cancer) occurred (day 60) in the 0.5 mg estradiol and 50 mg progesterone group. A descriptive lipid and coagulation factor summary (month 12) showed that estradiol–progesterone tended to decrease total cholesterol and low-density lipoprotein and increase triglycerides, with all factors within normal values.

The coprimary outcomes of vasomotor symptom frequency significantly decreased ($P<.05$) from baseline to weeks 4 and 12 with all doses of estradiol–progesterone compared with placebo (except for 0.5 mg estradiol and 50 mg progesterone at week 4; Fig. 3A) in the modified intent-to-treat vasomotor symptoms population. Reductions from baseline with 1 mg

Table 1. Participant Demographics and Baseline Characteristics (Safety Population)*

	Estradiol/Progesterone				
Characteristic	1 mg/100 mg	0.5 mg/100 mg	0.5 mg/50 mg	0.25 mg/50 mg	Placebo
n	415	424	421	424	151
Age (y)	54.7±4.4	54.5±4.5	54.9±4.3	54.4±4.0	54.5±4.3
Race					
White	271 (65.3)	281 (66.3)	276 (65.6)	273 (64.4)	100 (66.2)
African American	134 (32.3)	136 (32.1)	133 (31.6)	140 (33.0)	46 (30.5)
Other[†]	10 (2.4)	7 (1.6)	12 (2.8)	11 (2.6)	5 (3.3)
BMI (kg/m^2)	26.8±4.1	26.7±4.3	26.7±4.0	26.7±4.0	26.6±3.9
Time since menopause (y)	5.8±4.9	6.0±5.1	5.7±4.6	5.6±4.9	6.0±5.3
Bilateral oophorectomy	4 (1.0)	6 (1.4)	3 (0.7)	3 (0.7)	0
Baseline VMS parameters (VMS substudy)					
Weekly frequency	74.4±35.3	72.1±27.8	75.9±28.0	77.0±30.4	72.4±23.3
Weekly severity	2.54±0.32	2.51±0.25	2.50±0.23	2.51±0.26	2.52±0.25

BMI, body mass index; VMS, vasomotor symptoms.
Data are mean±SD or n (%) unless otherwise specified.
* Demographics and baseline characteristics were similar among groups.
[†] Other includes other (n=20), Asian (n=12), Native American or Alaska Native (n=6), Native Hawaiian or Pacific Islander (n=5), and unknown (n=2).

estradiol and 100 mg progesterone and 0.5 mg estradiol and 100 mg progesterone were 40.6 and 35.1 hot flushes, respectively, vs 26.4 with placebo at week 4, and 55.1 and 53.7 hot flushes, respectively, vs 40.2 at week 12. The coprimary endpoint of moderate-to-severe vasomotor symptom severity significantly decreased (improved) from baseline to week 4 with doses of 1 mg estradiol and 100 mg progesterone and 0.5 mg estradiol and 100 mg progesterone (by 0.48 and 0.51 points, respectively) compared with placebo (by 0.34) and to week 12 (by 1.12 and 0.90 points, respectively) compared with placebo (by 0.56); 0.5 mg estradiol and 50 mg progesterone significantly reduced severity better than placebo at week 12; and 0.25 mg estradiol and 50 mg progesterone

was not significantly different from placebo at either time point (Fig. 3B).

Significantly reduced vasomotor symptom frequency was first observed at week 3 for 1 mg estradiol and 100 mg progesterone, week 4 for 0.5 mg estradiol and 100 mg progesterone, week 6 for 0.5 mg estradiol and 50 mg progesterone, and week 3 for 0.25 mg estradiol and 50 mg progesterone (secondary efficacy endpoints; Fig. 3A). Significant vasomotor symptom severity reductions were first seen at week 3 for 1 mg estradiol and 100 mg progesterone and 0.5 mg estradiol and 100 mg progesterone (Fig. 3B). Based on Clinical Global Impression thresholds (secondary endpoint), clinical meaningfulness of the decreases in moderate-to-severe vasomotor symptoms

Table 2. Endometrial Safety Endpoints at 12 Months (Endometrial Safety Population)

	Estradiol/Progesterone				
Parameter, n (%)	1 mg/100 mg	0.5 mg/100 mg	0.5 mg/50 mg	0.25 mg/50 mg	Placebo
n	280	303	306	274	92
Hyperplasia at 12 mo					
Incidence rate	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
One-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)
Mo 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)
Mo 12	4 (1.4)	6 (2.0)	10 (3.3)	7 (2.6)	0 (0)

Data are n (%) unless otherwise specified.
* Active and disordered endometrial proliferation.

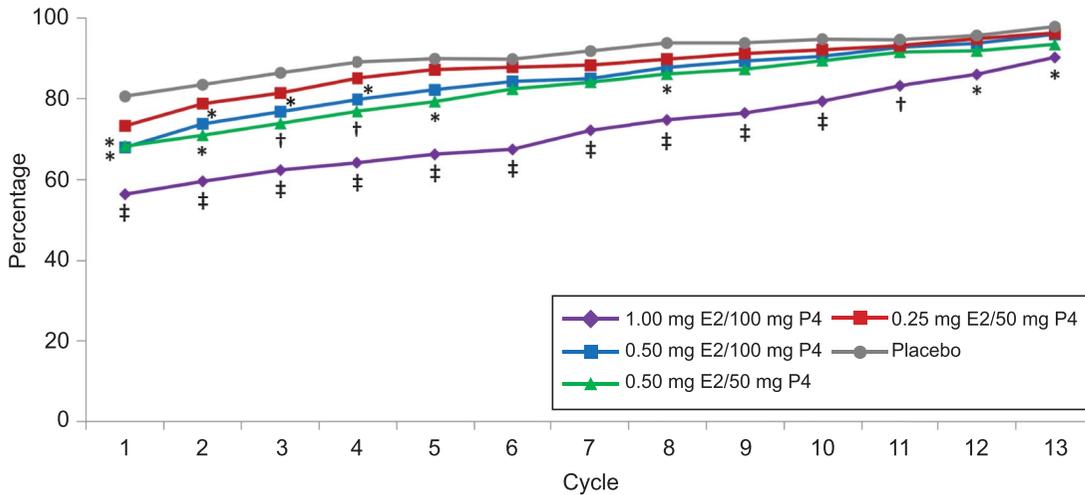**Fig. 2.** Rates of cumulative amenorrhea for cycles 1 to 13. *$P<.05$; †$P<.01$; ‡$P<.001$ vs placebo.
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was defined as 36 or less hot flushes at week 4 and 39 or greater hot flushes at week 12. Significantly more women had clinically meaningful reductions in vasomotor symptom frequency with estradiol–progesterone compared with placebo ($P<.05$ to $P<.001$) at week 4 (46–59% vs 33%) and week 12 (68–73% vs 52%).

DISCUSSION

Menopausal compounded HT use is prevalent in the United States, becoming standard of care based on prescription volume (surpassing FDA-approved HT[1]), potentially exposing women to risks of inadequately studied hormone preparations. This study found that TX-001HR, an oral, combined capsule of natural estradiol–progesterone, reduced moderate-to-severe vasomotor symptoms without causing endometrial hyperplasia. Two 17β-estradiol–progesterone doses (1 mg estradiol and 100 mg progesterone and 0.5 mg estradiol and 100 mg progesterone) significantly reduced vasomotor symptom frequency and severity by weeks 3 or 4; and 0.5 mg estradiol and 50 mg progesterone significantly reduced frequency by week 6 and severity at most time points from weeks 7–12. Clinically meaningful vasomotor symptom reductions were also found in more women taking estradiol–progesterone compared with placebo. In addition, amenorrhea rates were high and generally consistent with other approved HT products, and the uterine bleeding with all doses decreased over time. If approved, these data collectively support 17β-estradiol–progesterone meeting the needs of clini-

cians and women who prefer to prescribe or use a well-studied, FDA-approved, natural formulation.

REPLENISH results provide rigorous evidence for endometrial protection and efficacy in treating vasomotor symptoms with natural HT. Identifying progesterone doses that prevent endometrial stimulation with estradiol represents a major study finding; data on 100 mg progesterone given continuously are limited. Noteworthy, REPLENISH is the first, large, rigorous trial to demonstrate no endometrial hyperplasia with low doses of continuous oral progesterone (50 or 100 mg) plus different estradiol doses (based on a literature search conducted for randomized controlled studies of endometrial hyperplasia with HT containing progesterone [using PubMed from inception to December 2017 in English] using keywords progesterone, menopause, hyperplasia). The Postmenopausal Estrogen/Progestin Interventions trial of the 1990s was the only large, randomized, controlled trial before REPLENISH demonstrating endometrial protection with cyclic 200 mg progesterone plus conjugated equine estrogens.[16] The continuous nature of 17β-estradiol–progesterone may also be advantageous because several observational studies have shown no elevated or reduced risk of endometrial cancer with continuous HT with some reports suggesting that continuous compared with cyclic progestogen use may provide greater endometrial protection.[17,18]

All 17β-estradiol–progesterone doses were well tolerated with no clinically significant differences in adverse events or unexpected safety signals. Although some side effects were higher with

Table 3. Most Frequently Reported (3% of Women or Greater) Treatment-Emergent Adverse Events in Any Treatment Arm (Safety Population)

TEAE	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
Any TEAE*	297 (72)	302 (71)	293 (70)	288 (68)	78 (52)
Headache	31 (7.5)	24 (5.7)	45 (11)	43 (10)	4 (2.6)
Nasopharyngitis	25 (6.0)	41 (9.7)	37 (8.8)	24 (5.7)	4 (2.6)
Breast tenderness	45 (11)	19 (4.5)	25 (5.9)	10 (2.4)	1 (0.7)
Upper respiratory tract infection	22 (5.3)	26 (6.1)	34 (8.1)	15 (3.5)	6 (4.0)
Nausea	20 (4.8)	25 (5.9)	19 (4.5)	16 (3.8)	2 (1.3)
Back pain	22 (5.3)	11 (2.6)	15 (3.6)	15 (3.5)	1 (0.7)
Abdominal pain	22 (5.3)	10 (2.4)	14 (3.3)	15 (3.5)	4 (2.6)
Sinusitis	20 (4.8)	15 (3.5)	13 (3.1)	13 (3.1)	3 (2.0)
Dizziness	17 (4.1)	15 (3.5)	10 (2.4)	8 (1.9)	3 (2.0)
Pelvic pain	17 (4.1)	15 (3.5)	10 (2.4)	7 (1.7)	0
Diarrhea	13 (3.1)	13 (3.1)	11 (2.6)	11 (2.6)	2 (1.3)
Vulvovaginal mycotic infection	14 (3.4)	15 (3.5)	14 (3.3)	5 (1.2)	4 (2.6)
Abdominal distention	15 (3.6)	6 (1.4)	11 (2.6)	11 (2.6)	1 (0.7)
Vaginal discharge	16 (3.9)	13 (3.1)	7 (1.7)	7 (1.7)	1 (0.7)
Hypertension	7 (1.7)	13 (3.1)	9 (2.1)	12 (2.8)	2 (1.3)
Influenza	4 (1.0)	6 (1.4)	14 (3.3)	12 (2.8)	2 (1.3)
Vaginal bleeding	14 (3.4)	10 (2.4)	3 (0.7)	8 (1.9)	1 (0.7)
Any treatment-related TEAE	170 (41)	143 (34)	133 (32)	134 (32)	27 (18)
Any severe TEAE	26 (6.3)	30 (7.1)	26 (6.2)	24 (5.7)	4 (2.6)
Any discontinuation resulting from a TEAE	45 (11)	31 (7.3)	34 (8.1)	38 (9.0)	10 (6.6)
Any serious TEAE	9 (2.2)	13 (3.1)	8 (1.9)	8 (1.9)	2 (1.3)
Any treatment-related serious AE†	3 (0.7)	2 (0.5)	1 (0.2)	2 (0.5)	1 (0.7)
Acute pancreatitis	1 (0.2)	0	0	0	0
Breast cancer‡	2 (0.5)	2 (0.5)	1 (0.2)	1 (0.2)	0
Deep vein thrombosis	0	0	1 (0.2)	0	0
Chronic obstructive pulmonary disease	0	0	0	1 (0.2)	0
Infective cholecystitis	0	0	0	0	1 (0.7)

TEAE, treatment-emergent adverse event; AE, adverse event.

Data are n (%) unless otherwise specified.

* Occurring on or through 15 d posttherapy.

† Occurring on or posttherapy; serious AEs were life-threatening events or those requiring hospitalization, and based on medical judgment, jeopardized the patient and required medical or surgical intervention.

‡ Breast cancer includes invasive ductal breast cancer.

17β-estradiol–progesterone compared with placebo, these were not unexpected with oral HT. Changes in lipid and coagulation parameters were not clinically important, including triglycerides. Progesterone may have a different risk profile than synthetic progestins. Risks for venous thromboembolism[14] and breast cancer[12,13] have been shown to increase with estrogens plus synthetic progestins; however, European observational studies did not observe elevated venous thromboembolism[14] or breast cancer[12,13] risk with natural progesterone. Women taking 17β-estradiol–progesterone had an incidence of breast cancer (0.36% [6/1,684]) consistent with Surveillance, Epidemiology, and End Results data (0.29%)[19] and venous thromboembolism (0.06% [1/1,684]) consistent with U.S. population-based data (0.13%)[20] for women 40–64 years of age. Overall, the incidence and nature of the reported adverse events and serious adverse events were consistent with that expected in a postmenopausal population.

Limitations of this study include its shorter duration and studying a population of women healthier than the general population, although typical for phase 3 efficacy and safety vasomotor symptom trials, and investigation of only U.S. women. A discontinuation rate of approximately 30% is another limitation, but also typical for menopausal therapy studies of 1 year in duration.

Millions of women have been estimated yearly to take compounded HT in the United States.[1] However, to achieve endometrial protection, the ratio of progestogens to estrogens must be
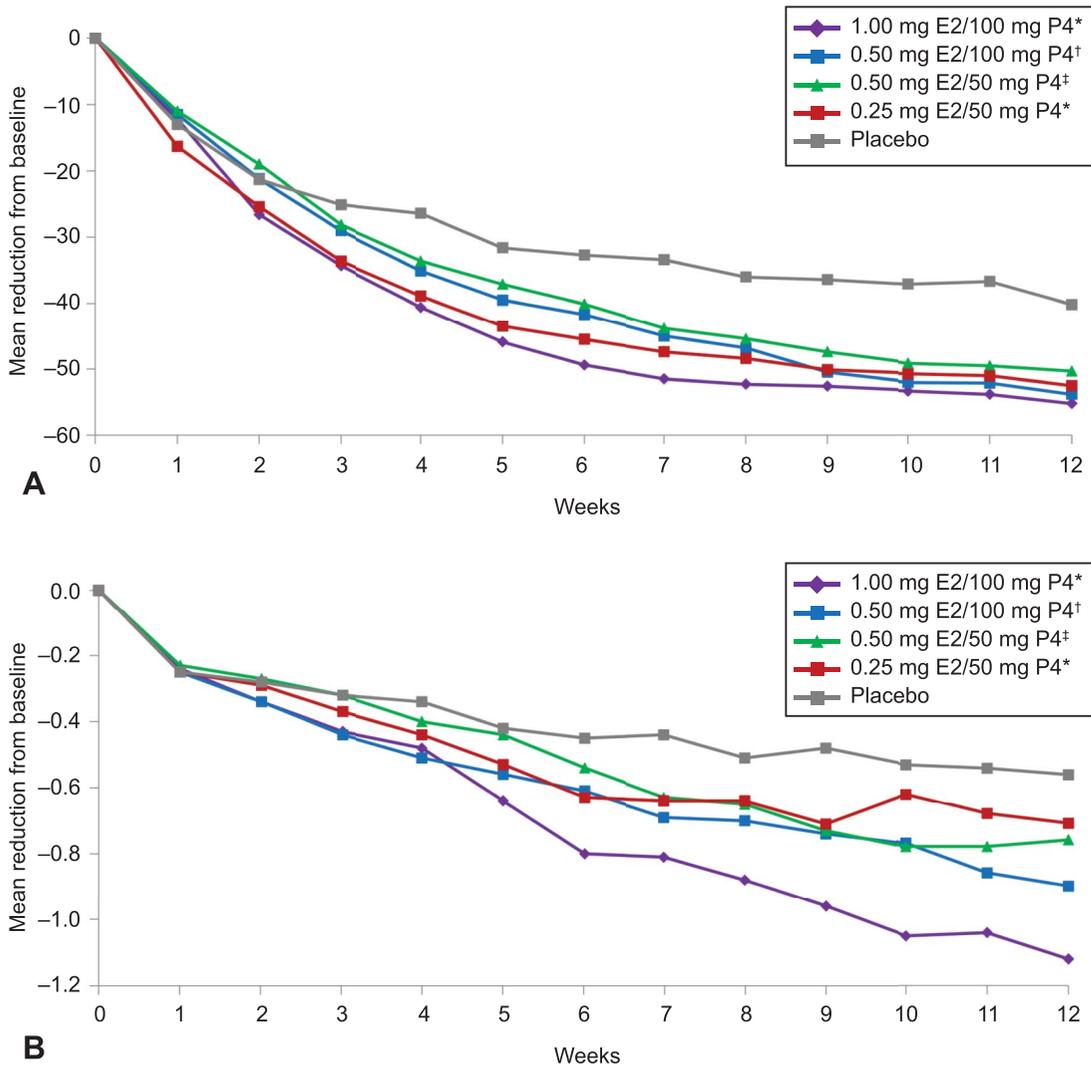
Fig. 3. Change in frequency (**A**) and severity (**B**) of moderate-to-severe vasomotor symptoms up to week 12 vs placebo (coprimary endpoints are at weeks 4 and 12). Frequency significantly different from placebo (*P*<.05) at *weeks 3–12; †weeks 4–12; ‡weeks 6–12. Severity significantly different from placebo (*P* <.05) at *weeks 3–12; †weeks 7, 9–12; ‡weeks 6, 7, 9.

Lobo. Oral 17β-Estradiol–Progesterone. Obstet Gynecol 2018.

appropriate in combined HT products.[8] Reports of endometrial cancer and hyperplasia in postmenopausal women taking compounded HT have been published (Dezman VL, et al. Int J Gynecol Cancer 2015;25(suppl 1):71.).[9,10] Given this potential risk and often missing or inappropriate safety warnings accompanying these formulations, medical societies advise against the use of compounded HT.[4,21,22] Additionally, FDA is taking action against false and misleading compounded HT claims and is encouraging consumers to become informed of these products and their risks.[23]

TX-001HR is the first, combined estradiol–progesterone formulation developed to treat moderate-to-severe postmenopausal vasomotor

symptoms. Combining estradiol and progesterone had previously been challenging, because of the differences in their structure and solubility.[24] Bioavailability of the combined estradiol and progesterone in 17β-estradiol–progesterone was not shown to be compromised compared with individual doses of commercially available reference estradiol and progesterone products.[24] A single-capsule, continuous-combined estradiol–progesterone (compared with cyclic) may be more convenient for women than separate capsules, potentially increasing adherence and consequently efficacy.[25,26] Based on these study results, TX-001HR may represent a new option, using natural hormones, for postmenopausal women, including the estimated

millions currently using inadequately studied, non–FDA-approved, compounded HT.

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