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ORIGINAL STUDY

Effects of combined 17β-estradiol and progesterone on weight and blood pressure in postmenopausal women of the REPLENISH trial

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Abstract

Objective: To examine the impact of a single-capsule 17β-estradiol (E2)/progesterone (P4) on weight and blood pressure (BP) when treating moderate to severe vasomotor symptoms in postmenopausal women with a uterus.

Methods: Healthy postmenopausal women with a uterus (aged 40-65, body mass index $\leq$34 kg/m^2, BP $\leq$140/90 mm Hg) were randomized to daily E2/P4 (mg/mg; 1/100, 0.5/100, 0.5/50, 0.25/50) or placebo in the phase 3 REPLENISH trial (NCT01942668). Changes in weight and BP from baseline to month 12 were evaluated. Potentially clinically important changes were defined as increases or decreases from baseline in weight by $\geq$15% and $\geq$11.3 kg, systolic BP by $\geq$20 mm Hg (absolute value $\geq$160 or $\leq$90 mm Hg), and diastolic BP by $\geq$15 mm Hg (absolute value $\geq$90 or $\leq$60 mm Hg).

Results: Overall mean changes in weight and BP from baseline to month 12 with E2/P4 were modest and generally not statistically or clinically significant versus placebo. Incidence of potentially clinically important changes was low for weight (E2/P4 vs placebo: 1.1-2.6% vs 2.2%), systolic BP (0.3-1.1% vs 1.1%), and diastolic BP (1.4-4.2% vs 3.2%). A small number of women had treatment-related, treatment-emergent adverse events of weight gain (1.4-2.6% vs 1.3%) or hypertension (0.2-1.2% vs 0%). Few women who discontinued E2/P4 had weight gain (1.6%) or hypertension (0.6%) as a primary reason. Efficacy profile on VMS was consistent with previous findings and not modified by body mass index.

Conclusions: Twelve-month use of E2/P4 had no clinically meaningful impact on weight or BP in postmenopausal women of the REPLENISH study.

Key Words: Blood pressure – Body mass index – Body weight – Estradiol – Progesterone – Vasomotor symptoms.

Although aging in women is often accompanied by increases in body weight, hormonal changes at menopause can have added effects, especially with central adipose distribution and abdominal obesity.[1-3] Many women choose not to initiate or discontinue hormone therapy (HT) due to their fear of undesired weight gain.[4,5] However, reviews of clinical studies generally show a neutral to beneficial effect of some HT formulations on body weight and fat distribution during menopause.[2,5-8] In fact, several studies showed that HT slowed down weight gain due to aging, as less weight gain was observed in postmenopausal women using some HT formulations compared with non-users,[9-14] and some studies even reported weight loss in women using HT.[15-17]

Aging is also associated with elevated blood pressure (BP).[18,19] Hypertension is one of the major risk factors for cardiovascular morbidity and mortality in postmenopausal women.[19-21] Hypertension was found to be more prevalent in older women, especially in those aged 60 years or more,[19,20] and associated with being overweight.[19] A positive relationship between hypertension and menopausal status in women has been suggested.[22,23] Estrogen deficiency in women may contribute to the rising BP during menopause.[20,21] Data regarding the effect of HT on BP are inconsistent, although most of the reported effects on BP are either neutral or beneficial.[6,18,21] Synthetic progestin in combined HT has been suggested to counteract the vasodilatory effects of estrogen, whereas natural progesterone (P4) may have a positive effect of lowering BP.[21]

An oral, single-capsule of combined bioidentical 17β-estradiol (E2) and P4, TX-001HR (TherapeuticsMD, Boca Raton, FL), was developed to treat moderate to severe vasomotor

symptoms (VMS) in postmenopausal women with a uterus. Of the four different doses of TX-001HR (E2/P4: 1 mg/100 mg, 0.5 mg/100 mg, 0.5 mg/50 mg, and 0.25 mg/50 mg) evaluated for safety and efficacy in the REPLENISH trial, the 1 mg/100 mg and 0.5 mg/100 mg doses significantly reduced the frequency and severity of moderate to severe VMS from baseline, meeting all co-primary endpoints, without negative impacts on endometrial safety[24] or cardiovascular outcomes.[25] Quality of life and sleeping profiles in postmenopausal women also improved with TX-001HR.[26,27] In addition, an easy-to-use, oral, single-capsule formulation may facilitate adherence in women.[28-30] The 1 mg E2/100 mg P4 dose was FDA approved as Bijuva ([E2 and P4] capsules, TherapeuticsMD, Boca Raton, FL) for the treatment of moderate to severe VMS in postmenopausal women with a uterus.

To address women's concern of weight gain when using menopausal HT, this paper reports weight and BP changes in women who used TX-001HR in the REPLENISH study and examines the possible influence of body mass index (BMI) on the efficacy of TX-001HR in treating VMS.

METHODS

Study design and participants

REPLENISH (NCT01942668) was a multicenter, randomized, placebo-controlled, double-blind, phase-3 trial evaluating TX-001HR for the treatment of moderate to severe VMS in postmenopausal women with a uterus. The trial was conducted in accordance with Good Clinical Practice at 117 US sites, with the study protocol approved by a central or local institutional review board at each study site. Healthy women with menopausal VMS and aged 40-65 years with an intact uterus, BMI $\leq 34 \text{ kg/m}^2$, and sitting BP $\leq 140/90$ mm Hg were eligible to enroll. Postmenopausal women were characterized as those who had spontaneous amenorrhea for ≥ 12 months or a screening serum follicle-stimulating hormone level >40 mIU/mL for ≥ 6 months, or bilateral oophorectomy 6 weeks or more prior to screening. Major exclusion criteria included having contraindication or allergy to estrogen and/or P4, heavy smoking (≥ 15 cigarettes/d), and recent use of medications that could alter P4 or estrogen activity. Women with a history of thromboembolic disorder, coronary artery or cerebrovascular disease, chronic liver or kidney disorder, diabetes, or other endocrinological diseases were also excluded. Women who used medications that could affect the outcome of the VMS endpoints within 28 days before screening were not eligible for the VMS substudy. Additional key inclusion and exclusion criteria, typical for menopausal HT studies, have been described elsewhere.[24] Written informed consent was obtained for all participants.

A reproducible, computer-generated block schedule was used to randomize participants to four daily, oral doses of E2 (mg)/P4 (mg) (1/100, 0.5/100, 0.5/50, 0.25/50) for 12 months.[24] Enrolled participants who had ≥ 7 moderate to severe hot flushes per day or ≥ 50 per week at screening were assigned into four active treatment groups and one placebo group equally in a modified-intent-to-treat VMS

(MITT-VMS) substudy. The remaining participants were randomized to the four active doses at 1:1:1:1. The safety population included all participants who took at least one dose of the study drug for analysis of drug safety. To ensure study blind, a double-dummy design was used.[24,25]

Efficacy and safety endpoints

Primary efficacy endpoints of the study were changes in frequency and severity of moderate to severe VMS from baseline to weeks 4 and 12 in the VMS substudy. Daily diaries of participating women were used to collect weekly hot flush frequency data (total number of moderate and severe hot flushes in the last 7 d) and a weekly hot flush severity score (calculated as [(number of mild hot flushes) $\times 1 +$ (number of moderate hot flushes) $\times 2 +$ (number of severe hot flushes) $\times 3$] / (total number of mild, moderate, and severe hot flushes)] over 7 d).

The primary safety endpoint was incidence of endometrial hyperplasia in women who completed the 12-month treatment, as previously reported.[24] Further safety assessments included vital signs (sitting BP, heart rate, respiratory rate, and body temperature), physical examination findings, body weight, and BMI.

In the safety population, vital signs and adverse events (AEs) were monitored throughout the study. Sitting BP was measured at screening, weeks 4, 8, and 12, and months 6, 9, and 12, whereas body weight was measured at screening, week 4, and months 6 and 12. Clinically significant worsening from baseline or new findings in vital signs were considered AEs. All nonserious AEs were collected after informed consent was signed through 15 days following the last dose and serious AEs were collected through 30 days after the last dose. Treatment-emergent adverse events (TEAEs) were collected from the time of the first dose through 15 days after the last dose, and were assessed for severity and causality with the study drug. Treatment compliance was assessed at week 12 for the MITT-VMS population and at month 12 for the safety population, and was calculated for all women regardless whether the woman completed or discontinued the study during the time periods. A compliant woman was defined as one who took $\geq 80\%$ of the capsules expected to be taken for the respective time periods (over the first 12 weeks or throughout the 1-year study). Compliance rates were determined as proportions of compliant women in the specific populations.

Statistical analysis

The overall sample size in this study was determined based on the target of achieving 1% or less incidence of endometrial hyperplasia after the 12-month therapy with an upper bound of 95% confidence of 4% or less. The size of the VMS substudy was based on the hypothesized changes in the frequency and severity of VMS from baseline to weeks 4 and 12. Demographic characteristics were summarized descriptively. Changes from baseline at screening to month 12 for sitting BP and body weight were analyzed for each time point and compared

TABLE 1. *Criteria for potentially clinically important (PCI) changes in vital signs and weight*

Variable	Criteria[a]
Sitting BP (Systolic)	Increase or decrease from baseline of $\geq$20 mm Hg with absolute value of $\geq$160 or $\leq$90 mm Hg
Sitting BP (Diastolic)	Increase or decrease from baseline of $\geq$15 mm Hg with absolute value of $\geq$90 or $\leq$60 mm Hg
Body weight	Increase or decrease from baseline of $\geq$15% and $\geq$11.3 kg

BP, blood pressure.

[a]Baseline was defined as the last value prior to treatment.

between each active treatment group versus placebo. Incidence of potentially clinically important (PCI) change was defined as the proportion of women who had BP or weight changes meeting the PCI criteria (Table 1). Mean changes in frequency and severity of VMS were analyzed by a mixed model for repeated measures method, where treatment, week, and treatment-by-week interaction as factors, baseline as covariate, and participant as repeated measures unit. Influence of BMI on VMS treatment response was analyzed across baseline BMI tertiles ($<25 \text{ kg/m}^2$, ≥25 and $<30 \text{ kg/m}^2$, and $\geq30 \text{ kg/m}^2$). Statistical analysis was performed with SAS v9.2 or higher (SAS Institute, Cary, NC).

RESULTS

Participants disposition and demographics

The safety population included all 1,835 participants who took at least one dose of the study drug during the study. The overall ratio of women who received E2/P4 vs women who received placebo was approximately 11:1 (Fig. 1). Demographic characteristics were similar between all groups (Table 2). Women had a mean age of 54.6 years, mean weight of 72.0 kg, mean BMI of 26.7 kg/m², and an average of 5.8 years since menopause. The majority (65.4%) of women were white and one-third (32.1%) African American (Table 2). At baseline, sitting BP measures were comparable across all groups, with mean systolic BP ranging from 118.9 to 120.5 mm Hg and mean diastolic BP 75.7 to 76.3 mm Hg.

A total of 726 women were included in the MITT-VMS substudy (efficacy population). The demographic characteristics of the VMS substudy were similar to those in the safety population.[24] Baseline mean VMS frequency ranged from 65.6 to 82.4 hot flushes per week. Baseline mean VMS severity scores were similar and ranged from 2.43 to 2.61 across treatment groups.

The compliance rate was 89.5% for the MITT-VMS population over the first 12 weeks and 76.3% for the safety population over the 1-year study period.

Changes in body weight

With 12-month use of study drug, mean body weight remained nearly unchanged compared with baseline in all treatment groups (Fig. 2A). In general, no statistically significant differences were observed in mean changes from baseline to month 12 with E2/P4 versus placebo; mean changes in all groups were <1 kg and not considered clinically meaningful, albeit statistically significant in the 0.5 mg/100 mg E2/P4 group (Table 3).
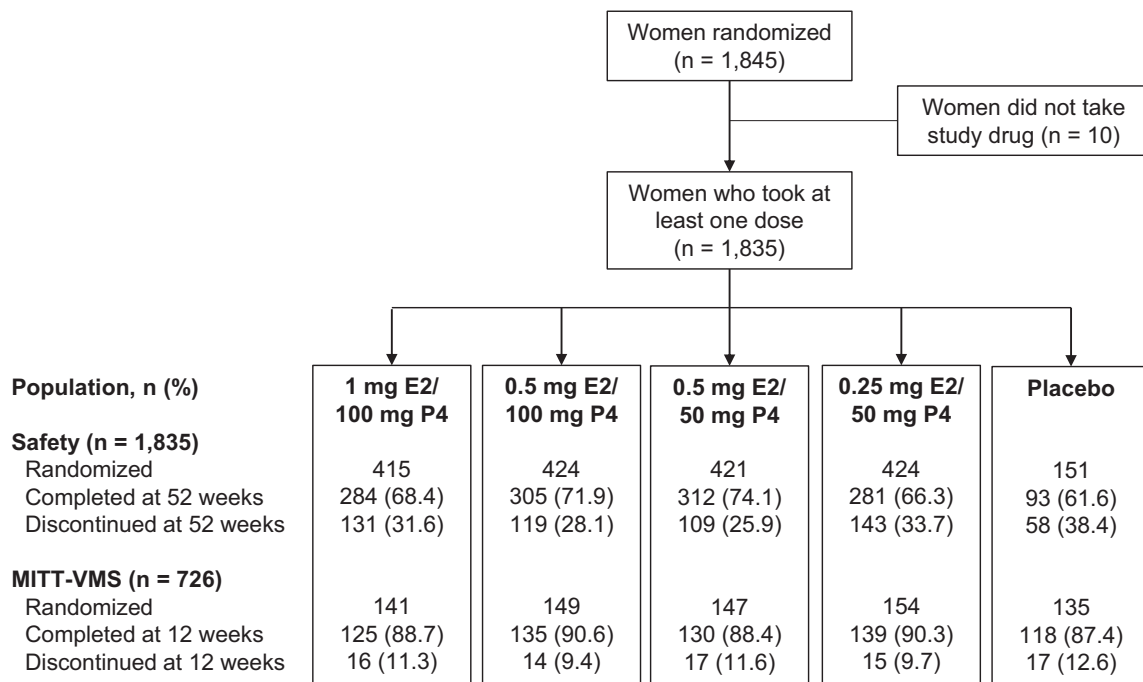

Population, n (%)	1 mg E2/ 100 mg P4	0.5 mg E2/ 100 mg P4	0.5 mg E2/ 50 mg P4	0.25 mg E2/ 50 mg P4	Placebo
Safety (n = 1,835)					
Randomized	415	424	421	424	151
Completed at 52 weeks	284 (68.4)	305 (71.9)	312 (74.1)	281 (66.3)	93 (61.6)
Discontinued at 52 weeks	131 (31.6)	119 (28.1)	109 (25.9)	143 (33.7)	58 (38.4)
MITT-VMS (n = 726)					
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)
Discontinued at 12 weeks	16 (11.3)	14 (9.4)	17 (11.6)	15 (9.7)	17 (12.6)

FIG. 1. Disposition of participants in the safety population and the MITT-VMS substudy. E2, 17β-estradiol; MITT-VMS, modified intent-to-treat vasomotor symptoms substudy; P4, progesterone.

TABLE 2. *Demographic and baseline characteristics*

Characteristic	E2 (mg)/P4 (mg)				Placebo (n = 151)	Total (n = 1,835)
	1/100 (n = 415)	0.5/100 (n = 424)	0.5/50 (n = 421)	0.25/50 (n = 424)		
Age, y	54.7 ± 4.4	54.5 ± 4.5	54.9 ± 4.3	54.4 ± 4.0	54.5 ± 4.3	54.6 ± 4.3
Race, n (%)						
White	271 (65.3)	281 (66.3)	276 (65.6)	273 (64.4)	100 (66.2)	1,201 (65.4)
Black or African American	134 (32.3)	136 (32.1)	133 (31.6)	140 (33.0)	46 (30.5)	589 (32.1)
Other[a]	10 (2.4)	7 (1.6)	12 (2.8)	11 (2.6)	5 (3.3)	45 (2.4)
Weight, kg	72.1 ± 12.3	71.7 ± 13.1	72.2 ± 11.8	72.1 ± 11.9	71.4 ± 11.5	72.0 ± 12.2
BMI, kg/m^2	26.8 ± 4.1	26.7 ± 4.3	26.7 ± 4.0	26.7 ± 4.0	26.6 ± 3.9	26.7 ± 4.1
Years since last menstrual period, y	5.8 ± 4.9	6.0 ± 5.1	5.7 ± 4.6	5.6 ± 4.9	6.0 ± 5.3	5.8 ± 4.9
Baseline BP	n = 415	n = 423	n = 421	n = 423	n = 151	n = 1,833
Systolic BP, mm Hg	119.5 ± 12.0	120.3 ± 11.7	120.5 ± 11.9	119.5 ± 11.2	118.9 ± 10.9	
Diastolic BP, mm Hg	75.7 ± 8.2	76.2 ± 8.0	76.3 ± 8.1	76.2 ± 8.1	75.9 ± 7.7	
Baseline VMS (MITT-VMS; BMI <25 kg/m^2)	n = 54	n = 49	n = 52	n = 58	n = 46	n = 259
Weekly frequency	80.4 ± 45.4	69.0 ± 21.4	75.9 ± 23.3	82.4 ± 35.3	73.0 ± 20.8	
Weekly severity	2.53 ± 0.25	2.53 ± 0.27	2.49 ± 0.23	2.59 ± 0.28	2.48 ± 0.27	
Baseline VMS (MITT-VMS; BMI ≥25 and <30 kg/m^2)	n = 56	n = 55	n = 64	n = 65	n = 61	n = 301
Weekly frequency	73.5 ± 23.1	70.3 ± 30.3	76.5 ± 30.8	72.0 ± 26.2	70.5 ± 25.4	
Weekly severity	2.61 ± 0.24	2.46 ± 0.25	2.48 ± 0.23	2.43 ± 0.21	2.54 ± 0.24	
Baseline VMS (MITT-VMS; BMI ≥30 kg/m^2)	n = 31	n = 45	n = 31	n = 31	n = 28	n = 166
Weekly frequency	65.6 ± 32.3	77.6 ± 30.3	74.6 ± 30.3	77.5 ± 27.9	75.7 ± 22.7	
Weekly severity	2.44 ± 0.50	2.56 ± 0.21	2.56 ± 0.24	2.54 ± 0.27	2.55 ± 0.23	

Data are mean ± SD unless noted otherwise.
BMI, body mass index; BP, blood pressure; E2, 17β-estradiol; MITT-VMS, modified intent-to-treat vasomotor symptoms substudy; P4, progesterone; SD, standard deviation; VMS, vasomotor symptoms.
[a]Other includes: Other (20), Asian (12), American Indian or Alaska Native (6), Native Hawaiian or Pacific Islander (5), and Unknown (2).

Similar percentages of women in the active (1.1%-2.6%) and placebo (2.2%) groups had changes in body weight meeting PCI criteria (Table 1) at month 12, with half of them having PCI weight gain and the other half having PCI weight loss (Table 3). In addition, the number of women having PCI weight gain was similar to that of women having PCI weight loss within each E2/P4 group (Table 3; Fig. 2B).

Changes in blood pressure

Mean sitting BPs (both systolic and diastolic) at month 12 were similar to those at baseline for any treatment group (Fig. 3A and B). Mean changes from baseline to month 12 ranged from 0.2 to 1.3 mm Hg in systolic BP and −0.4 to 0.4 mm Hg in diastolic BP, without showing any dose dependence in either measure (Table 3).

At month 12, no difference was found in the proportions of women having PCI changes in systolic or diastolic BP with E2/P4 vs placebo (1.4%-4.2% vs 3.2% for diastolic BP and 0.3%-1.1% vs 1.1% for systolic BP; Table 3). Both PCI increases and PCI decreases were observed within each treatment group for both systolic and diastolic BP, except for no PCI decrease in systolic BP in the 0.5 mg/100 mg E2/P4 and the placebo groups (Fig. 3C and D).

Discontinuation due to weight gain or hypertension

Related TEAEs of weight gain (E2/P4 vs placebo: 1.4%-2.6% vs 1.3%) and hypertension (0.2%-1.2% vs 0%) were reported in a small number of women during the study. Discontinuation rates due to these TEAEs were low. Among the 502 women who discontinued E2/P4, weight gain was the
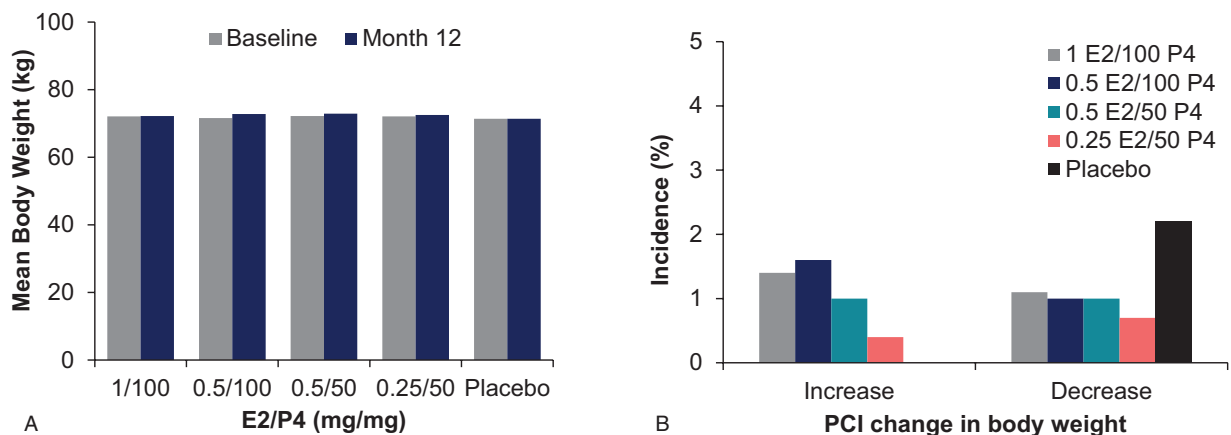

FIG. 2. Changes in weight from baseline to month 12. (**A**) Comparison of mean body weight at baseline and at month 12. (**B**) Comparison of incidence of PCI weight change in different treatment groups. E2, 17β-estradiol; P4, progesterone; PCI, potentially clinically important.

TABLE 3. *Changes from baseline to month 12 in body weight and blood pressure*

Measurement at month 12	E2 (mg)/P4 (mg)				Placebo (n = 151)	Total (n = 1,835)
	1/100 (n = 415)	0.5/100 (n = 424)	0.5/50 (n = 421)	0.25/50 (n = 424)		
Body weight	n = 282	n = 305	n = 312	n = 280	n = 93	n = 1,272
Mean change ± SD, kg	0.3 ± 4.4	0.7 ± 4.4	0.5 ± 4.3	0.3 ± 4.2	−0.3 ± 4.3	
P value (vs placebo)	0.249	0.032	0.133	0.113		
PCI change, n (%)	7 (2.5)	8 (2.6)	6 (1.9)	3 (1.1)	2 (2.2)	26 (2.0)
PCI increase, n (%)	4 (1.4)	5 (1.6)	3 (1.0)	1 (0.4)	0	13 (1.0)
PCI decrease, n (%)	3 (1.1)	3 (1.0)	3 (1.0)	2 (0.7)	2 (2.2)	13 (1.0)
Systolic BP	n = 284	n = 305	n = 312	n = 281	n = 93	n = 1,275
Mean change ± SD, mm Hg	1.0 ± 12.9	1.3 ± 12.9	0.2 ± 13.2	0.2 ± 13.0	1.2 ± 10.9	
P value (vs placebo)	0.679	0.993	0.528	0.577		
PCI change, n (%)	3 (1.1)	1 (0.3)	2 (0.6)	3 (1.1)	1 (1.1)	10 (0.8)
PCI increase, n (%)	1 (0.4)	1 (0.3)	1 (0.3)	2 (0.7)	1 (1.1)	6 (0.5)
PCI decrease, n (%)	2 (0.7)	0	1 (0.3)	1 (0.4)	0	4 (0.3)
Diastolic BP	n = 284	n = 305	n = 312	n = 281	n = 93	n = 1,275
Mean change ± SD, mm Hg	0.3 ± 8.8	0.4 ± 8.7	0.3 ± 9.6	−0.4 ± 8.6	0.2 ± 9.1	
P value (vs placebo)	0.745	0.911	0.965	0.568		
PCI change, n (%)	4 (1.4)	8 (2.6)	13 (4.2)	10 (3.6)	3 (3.2)	38 (3.0)
PCI increase, n (%)	1 (0.4)	5 (1.6)	5 (1.6)	3 (1.1)	2 (2.2)	16 (1.3)
PCI decrease, n (%)	3 (1.1)	3 (1.0)	8 (2.6)	7 (2.5)	1 (1.1)	22 (1.7)

BP, blood pressure; E2, 17β-estradiol; P4, progesterone; PCI, potentially clinically important; SD, standard deviation.

primary reason to withdraw for eight women (1.6%) and hypertension for three (0.6%).

Effect of BMI on VMS treatment efficacy

At week 12, both severity and frequency of VMS in E2/P4 groups decreased from baseline, with changes in some active groups statistically significant versus placebo within each BMI subgroup (Fig. 4). The efficacy profile did not vary by BMI (Fig. 4). The 1 mg/100 mg and 0.5 mg/100 mg E2/P4 doses showed numerically greater improvement than placebo in terms of VMS frequency and severity at weeks 4 and 12 for all BMI subgroups, except for a similar decrease in severity
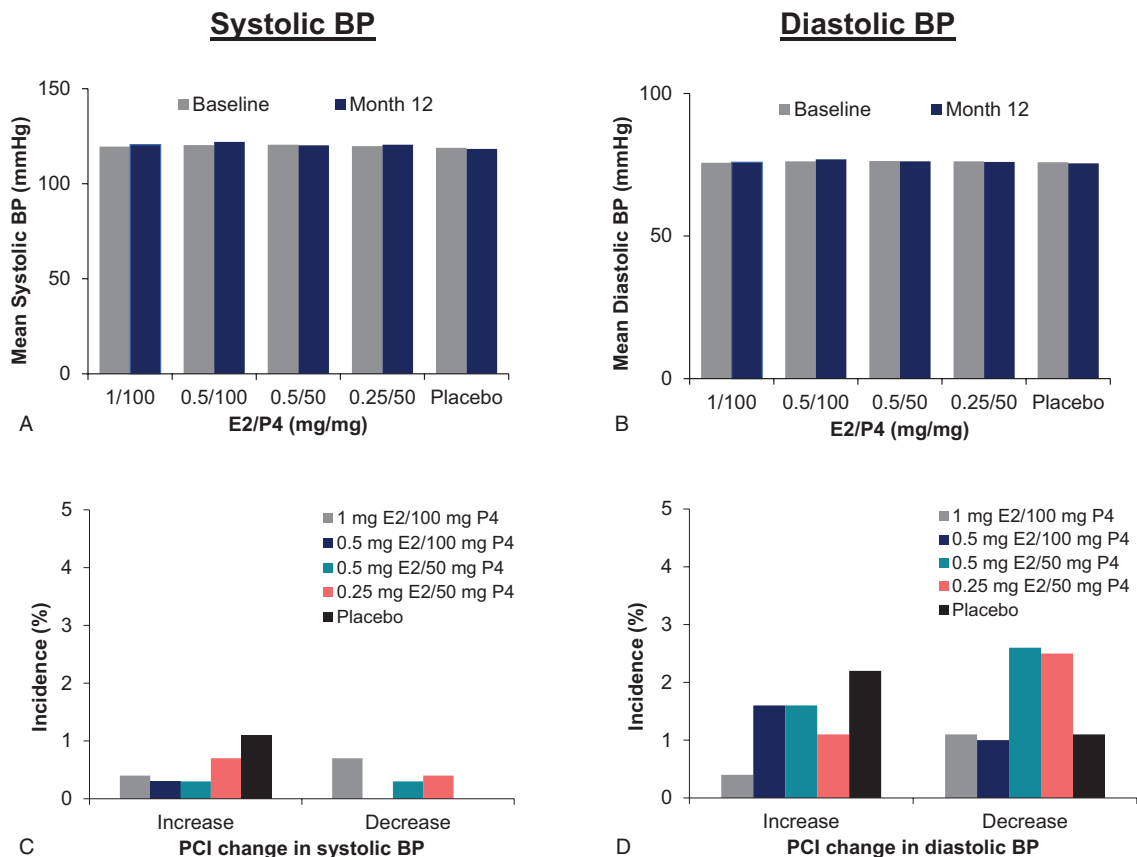

FIG. 3. Changes in sitting BP from baseline to month 12. Comparison of mean BP at baseline and at month 12 for systolic BP (**A**) and diastolic BP (**B**). Comparison of incidence of PCI changes in systolic BP (**C**) and diastolic BP (**D**). BP, blood pressure; E2, 17β-estradiol; MITT-VMS, modified intent-to-treat vasomotor symptoms substudy; P4, progesterone; PCI, potentially clinically important.
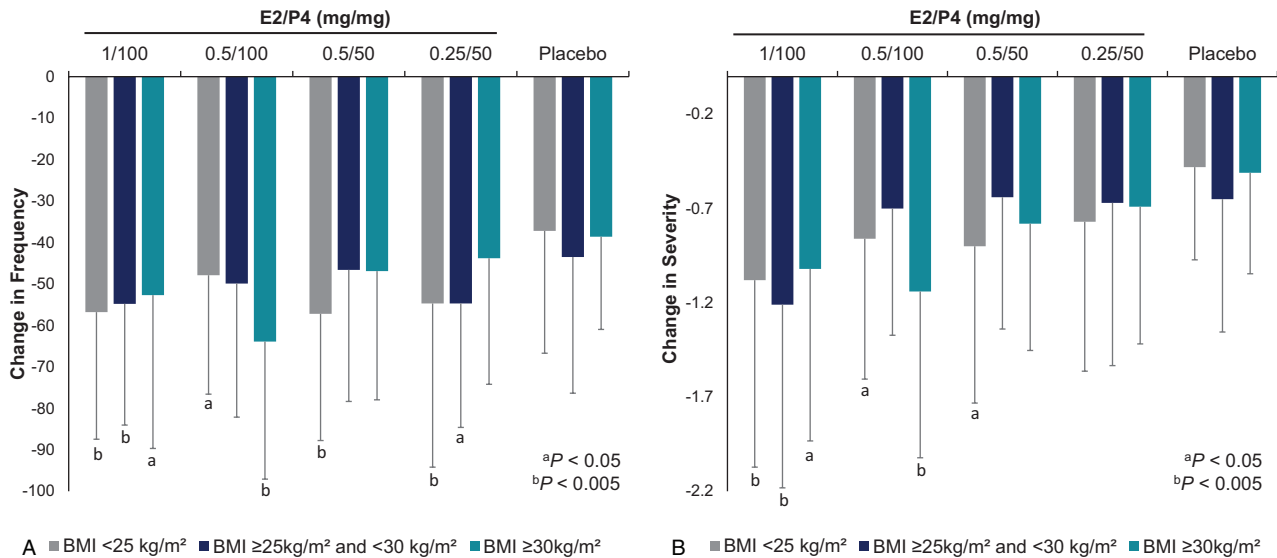
FIG. 4. Mean changes (±SD) from baseline in frequency (**A**) and severity (**B**) of moderate to severe VMS in different BMI subgroups at week 12. P value was calculated for each active dose versus placebo. BMI, body mass index; E2, 17β-estradiol; P4, progesterone; PCI, potentially clinically important; VMS, vasomotor symptoms.

for 1 mg/100 mg E2/P4 versus placebo at week 4 in the BMI $\geq 30 \, \text{kg/m}^2$ subgroup.

DISCUSSION

In the REPLENISH trial, mean changes in weight and BP at month 12 relative to baseline with E2/P4 were modest, without statistically significant differences in general, or clinically meaningful differences, when compared with placebo. The overall changes in each treatment groups were not substantial enough to be deemed clinically meaningful. Treatment-related TEAEs of weight gain or hypertension were reported at low frequencies and led to few study discontinuations. In addition, efficacy profiles of E2/P4 for relieving VMS within each BMI subgroup were found consistent with previous observation[24] and did not vary by BMI.

A common belief of women is that HT may bring undesired weight gain. Small gains in weight appear to be common in midlife women. Among women of 42-52 years who were participating in the Study of Women's Health Across the Nation, an average 2.1-kg increase in body weight over 3 years was observed.[31] In other randomized, controlled trials of HT in postmenopausal women, the observed mean weight gain was on average 0.4 to 1.6 kg in the placebo groups.[10,11,13] Mean weight of participants in REPLENISH remained relatively constant in all groups after 12 months of treatment. The mean changes from baseline in active groups were not significantly different versus placebo, except for the 0.5 mg/100 mg E2/P4 group, which could be a result of random variations by chance, as the changes showed no trends and the significant difference with 0.5 mg/100 mg E2/P4 was not observed at other time points during the study (data not shown).

Discontinuation due to weight gain occurred in a small percentage of the women (1.6%) who stopped using E2/P4. This is in contrast to HT with the more androgenic progestins,

which have been postulated to be associated with weight gain in postmenopausal women.[32] The results of no clinically meaningful weight gain after one year of TX-001HR use are consistent with previous systematic reviews showing no effect on body weight with combined estrogen and progestogen.[7,8]

Data in the Study of Women's Health Across the Nation study reported that higher BMI was associated with increased VMS in premenopausal or perimenopausal women.[33] However, such a correlation was not observed at baseline in the present study. The VMS substudy in REPLENISH excluded women with low levels of VMS and therefore may not be able to reflect any relationship between BMI and VMS. Effectiveness of HT with exogenous estrogen could also be modified by BMI. In the present study, the efficacy profile for relieving VMS among BMI subgroups was consistent with the primary analyses,[24] with the 1 mg/100 mg and 0.5 mg/100 mg E2/P4 mostly showing significant reductions in both frequency and severity of moderate to severe symptoms at weeks 4 and 12. This is in agreement with a previous observation in the Women's Health, Osteoporosis, Progestin, Estrogen study, which showed no significant impact of BMI on effectiveness in reducing VMS with conjugated estrogens/medroxyprogesterone acetate when the participants were grouped by BMI $<25 \, \text{kg/m}^2$ and BMI $\geq 25 \, \text{kg/m}^2$ ($P = 0.66$ for frequency and $P = 0.14$ for severity).[13]

BP is one of the risk factors for cardiovascular diseases.[6,34,35] Elevated BP is responsible for 51% of deaths from stroke and 45% from coronary heart disease according to the 2012 WHO World Health Statistics.[36] Therefore, prevention of unfavorable increases in BP is important for postmenopausal women. TX-001HR was not associated with changes in either systolic or diastolic BP in REPLENISH. This contrasts with the finding of a numerically small (1.35 mm Hg higher) but statistically significant difference in mean systolic BP between conjugated estrogens/medroxyprogesterone acetate and placebo arms at

year 1 in the Women's Health Initiative study.[37] The results here for REPLENISH are similar to those of the randomized, controlled postmenopausal estrogen/progestin interventions study, which found small increases in systolic BP with no significant differences among treatment groups including placebo.[9] In the large, randomized, controlled Danish Osteoporosis Prevention study of 17β-estradiol with or without norethisterone acetate, similar reductions in BP were observed in both HT users and nonusers,[38] whereas an observational cohort study in Australia showed an association of HT with significantly higher odds of having high BP.[39] Differences in design, sample size, type of hormones, or methods used for BP measurements could contribute to the inconsistency among these studies.[21]

Surrogate markers of cardiovascular disease risk include BP, weight, and lipids. Previous analyses reported from the REPLENISH study showed no clinically significant changes in risk parameters, including total cholesterol, triglycerides, and glucose, at month 12 with E2/P4 compared with placebo.[25] Together with the results on weight and BP from this analysis, the REPLENISH trial demonstrated that E2/P4 does not have adverse effects on cardiovascular disease risk factors.

One limitation of the study is that no data on waist-to-hip ratio or body composition were collected. Although weight gain might be mainly from aging, it is believed that hormonal changes during menopause transition result in a redistribution of body fat from lower body to central body.[1,2,40] The present analysis lacks the ability to evaluate counteracting effects by TX-001HR on menopause-related changes in adipose distribution. The study is also limited in that weight-affecting factors, such as diet, nutrition, and physical activity, were not controlled or evaluated in the study, although this is typical for trials evaluating HT. Nevertheless, the current analysis suggests that there were no clinically meaningful changes in weight and BP, adding to the safety information available for TX-001HR.

CONCLUSION

Data from the randomized, placebo-controlled, phase 3 REPLENISH trial revealed no overall clinically significant changes in body weight and sitting BP in all groups, showing no impact of TX-001HR on these cardiovascular disease risk factors. Together with previously reported efficacy and safety data,[24,25] the results of this analysis on weight and BP add to the efficacy and safety profile for the approved 1 mg/100 mg E2/P4 dose, which is an option for postmenopausal women with a uterus and moderate to severe VMS.

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