

ORIGINAL STUDY

17 β -estradiol/progesterone in a single, oral, softgel capsule (TX-001HR) significantly increased the number of vasomotor symptom-free days in the REPLENISH trial

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Abstract

Objective: To examine responder rates and vasomotor symptom-free days with oral 17 β -estradiol/progesterone (E2/P4; TX-001HR) versus placebo in the REPLENISH trial.

Methods: REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial, evaluating single, oral, softgel E2/P4 capsules in postmenopausal women (40-65 y) with a uterus and vasomotor symptoms (VMS). Women with moderate to severe hot flushes ($\geq 7/d$ or $\geq 50/wk$) were randomized (VMS substudy) to daily E2/P4 (mg/mg) of 1/100, 0.5/100, 0.5/50, 0.25/50, or placebo. Proportions of women with $\geq 50\%$ or $\geq 75\%$ reductions in moderate to severe VMS (responders), and those with no severe VMS as well as the weekly number of days without moderate to severe VMS with TX-001HR versus placebo were determined. Mixed model repeated measures was used to analyze data and Fisher exact test was employed to compare E2/P4 versus placebo.

Results: Seven hundred twenty-six women were eligible for the VMS efficacy analysis (E2/P4 1/100 [$n = 141$], 0.5/100 [$n = 149$], 0.5/50 [$n = 147$], 0.25/50 [$n = 154$], or placebo [$n = 135$]). Significantly more women treated with all E2/P4 doses versus placebo were $\geq 50\%$ responders and $\geq 75\%$ responders at weeks 4 and 12 ($P < 0.05$) and also had significantly more days per week without moderate to severe VMS at week 12 (1.9-3.0 d for E2/P4 versus 1.3 d for placebo; $P < 0.05$). The proportion of women without severe hot flushes at week 12 was 43% to 56% for all E2/P4 doses versus 26% for placebo ($P \leq 0.01$).

Conclusions: Women treated with E2/P4 had a greater response to treatment with more VMS-free days than with placebo. The E2/P4 1/100 dose (Bijuva [E2 and P4] capsules) represents an oral treatment option for postmenopausal women with moderate to severe VMS and a uterus.

Key Words: Hot flushes – Menopausal – Estradiol – Progesterone – Frequency – Vasomotor – Severity.

Menopausal women commonly experience vasomotor symptoms (VMS), vaginal dryness/dyspareunia, and difficulty sleeping/insomnia.¹ Although most women going through menopause experience VMS, severity, frequency, and duration can vary widely.¹ In the Study of Women's Health Across the Nation study, the mean duration of VMS was 5-7 years, but for some women their VMS may last up to 11 years² or even longer. VMS are often

bothersome to women³⁻⁵ and can negatively impact their quality of life,^{3,6} sleep,^{3,7} and work productivity.^{6,8}

Hormone therapy (HT) is the gold standard for relief of bothersome VMS in women who have no contraindication, as it reduces the frequency and severity of VMS.⁹ The North American Menopause Society recommends that the lowest HT dose providing symptom relief should be used.⁹ For women with a uterus, HT can be provided by prescribing a systemic estrogen

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Healthcare, and TherapeuticsMD. Dr. Bitner is on the speaker's bureau of TherapeuticsMD. Dr. Constantine consults to multiple pharmaceutical companies including but not limited to TherapeuticsMD, and has stock options from TherapeuticsMD. Dr. Bernick, Dr. Graham and Dr. Mirkin are employees of TherapeuticsMD with stock/stock options.

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(oral, transdermal patch, spray, gel, or vaginal rings) with a progestogen (oral, transdermal [combined patch], intrauterine system, injectable, and vaginal gels or tablets).⁹ In October 2018, an HT formulation combining 1 mg 17 β -estradiol (E2) and 100 mg progesterone (P4), in a single oral softgel capsule, was approved by the Food and Drug Administration (Bijuva [E2 and P4] capsules, TherapeuticsMD, Boca Raton, FL).¹⁰

The safety and efficacy of four different doses of the oral E2/P4 capsules (TX-001HR, TherapeuticsMD, Boca Raton, FL) were evaluated in the 12-week REPLENISH trial, in postmenopausal women with a uterus who were experiencing bothersome VMS.¹¹ Compared with placebo, the two highest E2/P4 doses (1/100 mg/mg and 0.5/100 mg/mg) demonstrated significant reductions in the frequency and severity of moderate to severe VMS at the coprimary endpoints of weeks 4 and 12, while protecting the endometrium from hyperplasia (safety endpoint).¹¹ The objectives of this analysis were to examine the response rates of women to treatment and to determine the number of VMS-free days with E2/P4 versus placebo in the REPLENISH trial.

METHODS

Study design

The REPLENISH trial (NCT01942668) was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in postmenopausal women with a uterus. Women were enrolled from 117 sites in the United States, beginning in August 2013; the last participant completed the trial in October 2016. The study was designed, conducted, and monitored in accordance with ethical guidelines of Good Clinical Practice and the Declaration of Helsinki, and all participants gave written informed consent.

Inclusion and exclusion criteria have been previously published.¹¹ Briefly, eligible participants were healthy postmenopausal women who were 40–65 years, had a body mass index of ≤ 34 kg/m², had an intact uterus, and were seeking treatment for VMS. Menopausal status was defined as ≥ 12 months of spontaneous amenorrhea, ≥ 6 months of amenorrhea with follicle-stimulating hormone > 40 mIU/mL, or ≥ 6 weeks postbilateral oophorectomy. Candidates were excluded if they had a history of thromboembolic disorder, coronary artery or cerebrovascular disease, clotting disorder, chronic liver or kidney disease, endocrinologic disease including diabetes, estrogen-dependent neoplasia, endometrial hyperplasia or unexplained vaginal bleeding, significant uterine fibroids, uterine ablation, or cancer history including melanoma, breast, uterine, or ovarian cancer. Heavy smokers (≥ 15 cigarettes per day) or those with drug or alcohol abuse history (within 1 y) were to be excluded. Participants couldn't have any contraindications or allergy to estrogens, progestins, or P4. Recent hormone use was prohibited, including estrogen pellets or injected progestational drugs (within 6 mo), intrauterine device (within 12 wk), estrogen in any dosage route (oral, transdermal, vaginal) with or without a progestin (8 wk), selective estrogen-receptor modulator (8 wk), or androgen preparation (8 wk); and any medication known to be a CYP3A4 enzyme inhibitor or inducer (within 4 wk), or any medications

that could alter estrogen or P4 activity or were intended to treat VMS (including over-the-counter drugs) were prohibited within 4 weeks before the study. These excluded medications were also prohibited during the study. Women in the VMS substudy could not have any recent use (within 28 d of screening) of medications that may affect VMS endpoints (eg, antidepressants, dopaminergic drugs, anticonvulsants, or clonidine).

Women with ≥ 7 moderate to severe VMS per day (or ≥ 50 per week) at baseline were enrolled in the 12-week VMS efficacy substudy and randomized 1:1:1:1 to oral E2/P4 (mg/mg) 1/100, 0.5/100, 0.5/50, or 0.25/50, or placebo; those with less severe or fewer hot flushes were randomized 1:1:1:1 to E2/P4 doses as participants in the safety study. Randomization was performed using a computer-generated block randomization schedule with a block size of 5, stratified by treatment arm within study sites. Given that different study doses had different capsule sizes, a double-dummy technique was used. All investigators and participants were blinded to study medications. Participants self-administered blinded study drug (2 capsules) daily at bedtime with food for 12 months. Treatment doses were chosen based on the lowest effective doses reported in the literature. The 1 and 0.5 mg doses of E2 have been previously shown to be effective for the treatment of VMS.¹² These E2 doses were combined with 100 or 50 mg of P4, as these doses taken continuously were expected to provide endometrial protection similar to the 200 mg P4 taken sequentially 12 d/cycle.

All women completed diaries recording the number and severity of her hot flushes through week 12. For assessments of VMS efficacy, the modified intent-to-treat (MITT) population included all randomized women who took at least 1 dose of study drug and had VMS frequency and severity data from diaries at baseline and for at least 1 week of treatment.

Study endpoints

The REPLENISH trial efficacy outcomes included four coprimary endpoints: mean change in frequency and severity of moderate to severe hot flushes from baseline to weeks 4 and 12 with each E2/P4 dose versus placebo in the MITT-VMS population. Results of these primary efficacy endpoints (as well as the primary safety endpoints) of the REPLENISH trial have been published.^{11,13,14}

Analyses of VMS were conducted in the MITT-VMS substudy population. Severity of hot flushes was defined as mild (sensation of heat without sweating), moderate (sensation of heat with sweating, but able to continue activity), or severe (sensation of heat with sweating, requiring cessation of activity). A baseline weekly severity score was calculated as the ([number of *moderate* hot flushes x 2] plus the [number of *severe* hot flushes x 3]) divided by the (total number of *moderate and severe* hot flushes) all over a period of 7 days. On treatment weekly severity scores were calculated as the ([number of *mild* hot flushes x 1] plus the [number of *moderate* hot flushes x 2] plus the [number of *severe* hot flushes x 3]) divided by the (total number of *mild, moderate, and severe* hot flushes) all over a period of 7 days.

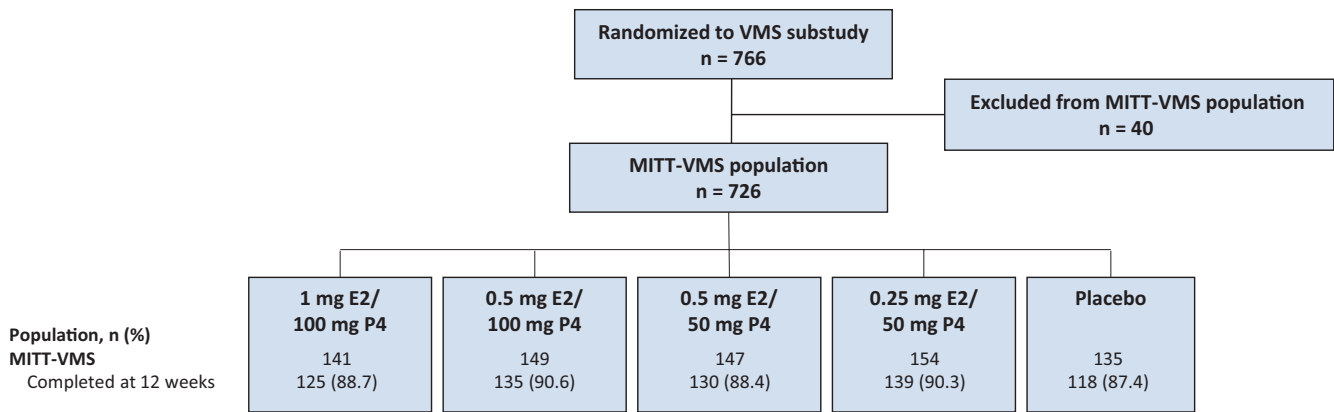


FIG. 1. Disposition of participants in the modified intent-to-treat-vasomotor symptoms efficacy study. E2, 17 β -estradiol; MITT, modified intent-to-treat; P4, progesterone, VMS, vasomotor symptoms.

Responder rates were calculated, with responders defined as women who had at least 50% or 75% reductions in moderate to severe VMS frequency (prespecified secondary endpoint). Other secondary (post hoc) endpoints were the number of days with no moderate to severe VMS and the proportion of women with no severe VMS at each study week.

Statistical analysis

Sample size for the VMS substudy was based on assumptions of a mean reduction in the weekly frequency of moderate to severe VMS of ≥ 56 from baseline to weeks 4 and 12 with any active treatment (versus 35 with placebo) and a reduction in severity of any hot flushes of ≥ 0.7 from baseline with any active treatment (vs 0.4 with placebo).¹¹ Therefore, approximately 750 women were to be randomized; a sample size of 150 women per group (active treatments or placebo) would provide at least 90% power to test the primary endpoints, allowing for a discontinuation rate of 20%.

Comparison of E2/P4 doses versus placebo were analyzed using a mixed effects model for repeated measures with baseline as covariate; treatment, study week, and treatment-by-study week interaction as fixed factors; and participant as

the repeated measure unit. Missing or invalid data were not imputed. Fischer exact tests were used to compare E2/P4 doses versus placebo.

RESULTS

Participants

A total of 1,845 women were randomized to study treatment and 766 were included in the VMS substudy (Fig. 1). Ten women did not take any investigational drug, leaving 1,835 randomized participants who took the study drug (MITT). Forty women were excluded from the analyses because of missing baseline and/or postbaseline diary data ($n = 34$); not receiving study drug or missing ≥ 2 doses or missing postbaseline diary data ($n = 5$); and protocol error (randomized twice; $n = 1$), leaving 726 women in the MITT-VMS population. Overall, 647 women (89%) completed the 12-week VMS substudy.

Women in the MITT-VMS population had a mean age of 55 years (range, 40–65 y), mean body mass index of 27 kg/m², mean time since menopause of 6 years, and race was predominantly white (67%) or African American (31%; Table 1). At baseline, women reported 72–77 moderate to severe VMS per week with an average severity score of 2.5.

TABLE 1. Demographics and baseline characteristics in the modified intent-to-treat vasomotor symptom population

| Characteristic | Estradiol/Progesterone (mg/mg) | | | | |
|-------------------------------|--------------------------------|-----------------------|----------------------|-----------------------|-----------------------|
| | 1/100 ($n = 141$) | 0.5/100 ($n = 149$) | 0.5/50 ($n = 147$) | 0.25/50 ($n = 154$) | Placebo ($n = 135$) |
| Age, y | 54.7 \pm 4.8 | 54.9 \pm 4.5 | 54.8 \pm 4.6 | 54.5 \pm 3.8 | 54.3 \pm 4.3 |
| Race, n (%) | | | | | |
| White | 95 (67.4) | 99 (66.4) | 99 (67.3) | 102 (66.2) | 91 (67.4) |
| Black | 45 (31.9) | 48 (32.2) | 43 (29.3) | 48 (31.2) | 41 (30.4) |
| Other ^a | 1 (0.7) | 2 (1.3) | 5 (3.4) | 4 (2.6) | 3 (2.2) |
| BMI, kg/m ² | 26.5 \pm 3.9 | 27.1 \pm 4.3 | 26.6 \pm 3.9 | 26.4 \pm 4.0 | 26.6 \pm 3.8 |
| Time since menopause, y | 6.1 \pm 5.5 | 6.5 \pm 5.4 | 6.0 \pm 4.8 | 5.2 \pm 4.8 | 5.7 \pm 4.9 |
| Bilateral oophorectomy, n (%) | 3 (2.1) | 3 (2.0) | 1 (0.7) | 1 (0.6) | 0 |
| Moderate to severe VMS | | | | | |
| Weekly frequency | 74.4 \pm 35.3 | 72.1 \pm 27.8 | 75.9 \pm 28.0 | 77.0 \pm 30.4 | 72.4 \pm 23.3 |
| Weekly severity | 2.54 \pm 0.32 | 2.51 \pm 0.25 | 2.50 \pm 0.23 | 2.51 \pm 0.26 | 2.52 \pm 0.25 |

Data expressed as mean \pm SD, unless specified otherwise.

BMI, body mass index; SD, standard deviation; VMS, vasomotor symptoms.

^aOther includes: other ($n = 10$), American Indian or Alaska Native ($n = 2$), Native Hawaiian or Pacific Islander ($n = 2$), and unknown ($n = 1$).

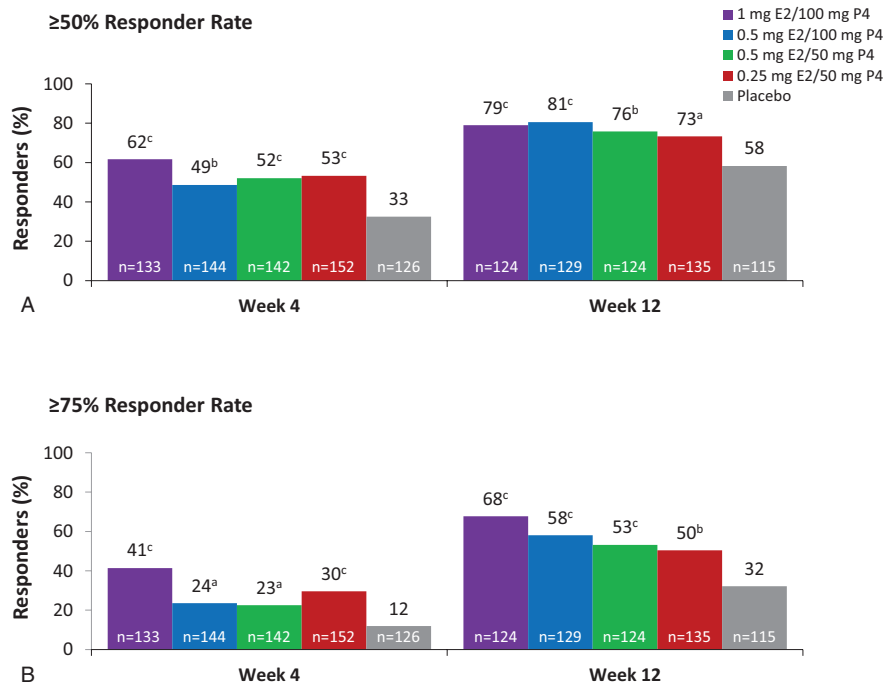


FIG. 2. Treatment response rates (A) 50% and (B) 75% at weeks 4 and 12. Response rates were defined as the proportion of women with $\geq 50\%$ and $\geq 75\%$ reductions in frequency of moderate to severe vasomotor symptoms by treatment. ^a $P < 0.05$; ^b $P < 0.01$; ^c $P \leq 0.001$ versus placebo (Fischer exact test). E2, 17 β -estradiol; P4, progesterone.

Change in moderate and severe vasomotor symptoms Responder rates

The percentage of women who responded to E2/P4 increased over time. Compared with placebo, significantly more women randomized to E2/P4 responded to treatment at weeks 4 and 12 (time of the coprimary endpoint analyses; Fig. 2). At week 4, approximately half of the women (49%-62%) taking E2/P4 had at least a 50% reduction in their weekly moderate to severe VMS (vs 33% for placebo; all, $P < 0.01$), this proportion increased to approximately three quarters of women (73%-81%) by week 12 (vs 58% for placebo; all, $P < 0.05$). The proportion of women with at least a 75% reduction in their weekly moderate to severe VMS

was 23%-41% for those randomized to E2/P4 compared with 12% for placebo at week 4 (all, $P < 0.05$), increasing to 50%-68% with the E2/P4 doses, and 32% with placebo at week 12 (all, $P < 0.01$).

Moderate to severe VMS-free days

From baseline to week 12, the mean number of days per week with no moderate to severe VMS steadily increased for all E2/P4 doses and placebo (Fig. 3). At week 12, women treated with any of the E2/P4 doses had significantly more days per week without moderate to severe VMS compared with placebo (1.9-3.0 d for E2/P4 groups vs 1.3 d for placebo; all, $P < 0.05$). Significant differences ($P < 0.05$) were detected as

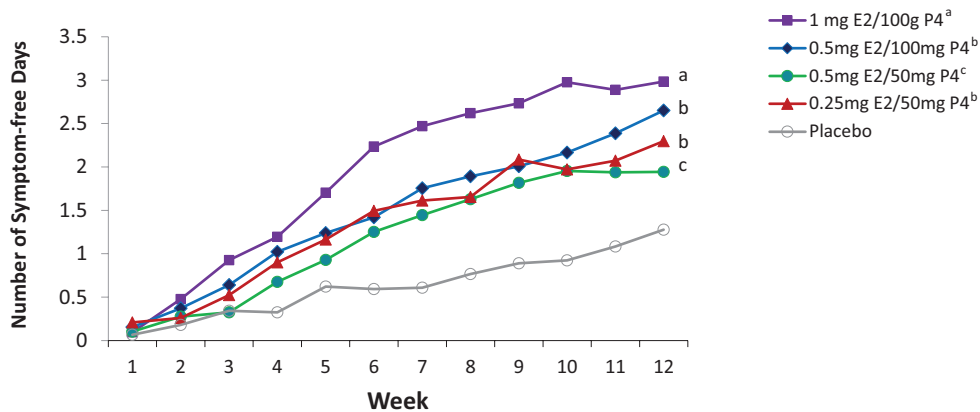


FIG. 3. Number of days per week free of moderate to severe vasomotor symptoms up to week 12 by E2P4 dose versus placebo. $P < 0.05$ from ^aweeks 3-12; ^bweeks 4-12; ^cweeks 6-12 versus placebo (Fischer exact test). E2, 17 β -estradiol; P4, progesterone.

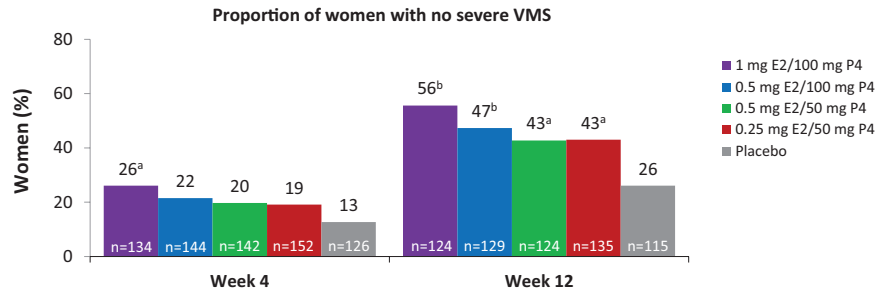


FIG. 4. Proportion of women with no severe vasomotor symptoms at weeks 4 and 12 by treatment. Severe VMS was defined as sensation of heat with sweating that requires cessation of activity. ^a $P \leq 0.01$; ^b $P < 0.001$ versus placebo (Fisher exact test). E2, 17 β -estradiol; P4, progesterone; VMS, vasomotor symptoms.

early as week 3 for the highest E2/P4 dose (1/100), at week 4 for the 0.5/100 and 0.25/50 doses and at week 6 for the 0.5/50 dose.

Proportion of women with no severe VMS

At week 12, significantly more women randomized to E2/P4 (43%-56%) had no severe VMS compared with placebo (26%; all, $P \leq 0.01$; Fig. 4). At week 4, compared with placebo, significantly more women taking the highest E2/P4 dose had no severe VMS ($P \leq 0.01$). Significant differences ($P < 0.05$) between E2/P4 versus placebo were detected as early as week 3 for the highest E2/P4 dose (1/100), at week 9 for the 0.5/100 and 0.5/50 doses and at week 5 for the 0.25/50 dose.

DISCUSSION

In the REPLENISH trial, E2/P4 decreased the frequency and severity of VMS; significantly more women taking oral E2/P4 softgel capsules responded to treatment and had no severe VMS, and women taking E2/P4 had more VMS-free days than those taking placebo. For women who received the E2/P4 1/100 or 0.5/100 dose, ~80% had at least a 50% decrease and 68% and 58%, respectively, had at least a 75% decrease in their moderate to severe VMS, all of which were significantly greater than with placebo. After 12 weeks of treatment, women who received the 1/100 dose or the 0.5/100 dose had ~3 days per week with no moderate to severe VMS and 56% and 47%, respectively, of the women no longer had any severe VMS.

All trials evaluating efficacy of treatment for moderate to severe VMS for a drug approval measure improvements of VMS frequency and severity in postmenopausal women with frequent VMS. However, only a few have assessed the effect of treatment on hot flush symptom-free days¹⁵ and proportions of women who are symptom free.¹⁵⁻¹⁷ Our study results on VMS symptom-free days were similar to those observed in a clinical trial evaluating symptom-free days with conjugated equine estrogens (CE)/bazedoxifene (BZA).¹⁵ No other trials have evaluated symptom-free days in this manner. The proportions of responders, defined as those without hot flushes, reported in our study were also similar to those reported for other menopausal hormone therapies. Two studies evaluated the proportion of women who had no more hot

flushes with HT use. In one study, women taking daily 0.6 mg CE reported 82% of days and 85% of nights without hot flushes during a one-year treatment, whereas those taking daily 10 mg medroxyprogesterone acetate reported 90% of days and 87% of nights were without hot flushes.¹⁶ In the other study, the percentage of women who were free of hot flushes during 3 months of continuous E2 use combined with 3-days-off/3-days-on pulsed norgestimate ranged between 70% and 76% with 1 mg E2 either alone or combined with 30, 90, or 180 microg norgestimate.¹⁷ In the trial evaluating CE/BZA, the percentage of women who had no moderate to severe (25%-41% vs 6%) or severe (50%-71% vs 33%) hot flushes was significantly greater with CE/BZA than placebo at week 12.¹⁵

These post hoc analyses of symptom-free days are consistent with the trial's primary efficacy results, which demonstrated that the two highest E2/P4 doses provided significant and clinically meaningful improvements in VMS frequency and severity compared with placebo.^{11,18} Greater numbers of moderate to severe VMS-free days and women without severe symptoms could likely have contributed to improvements in other secondary endpoints collected during the study, such as the Menopause Specific Quality of Life questionnaire and the Medical Outcome Study (MOS)-Sleep questionnaire. Quality of life as measured by the Menopause Specific Quality of Life questionnaire significantly improved with E2/P4 versus placebo,¹⁹ and significant improvements in sleep as measured by the MOS-Sleep questionnaire were reported in women randomized to E2/P4 compared with placebo.²⁰ Most of the E2/P4 doses significantly improved the MOS-Sleep total score, Sleep Problems Index I and II, and sleep disturbance subscale versus placebo from baseline to week 12, and up to year 1.²⁰ Although somnolence has been a concern with the use of P4,^{21,22} the MOS somnolence subscale was not negatively affected and somnolence incidence was low (0.2%-1.2%) with E2/P4 treatment.²⁰

Primary data from the trial also showed that E2/P4 had good safety and bleeding profiles, with the continuous doses of P4 protecting the endometrium during use of E2.^{11,13,14} The REPLENISH trial was a large, well-designed, randomized, placebo-controlled trial; however, limitations of this report were that analyses of symptom-free days were performed

posthoc and women in this study were generally healthier than those from the general population.

CONCLUSIONS

The REPLENISH trial evaluated E2/P4 in single, oral, softgel capsules. Women treated with E2/P4 1/100 or 0.5/100 doses had significant increases in the numbers of VMS-free days compared with women who received placebo. More women given E2/P4 versus placebo had at least a 50% or 75% reduction in their moderate to severe VMS. The E2/P4 1/100 dose (Bijuva) is an appropriate oral treatment option for moderate to severe VMS due to menopause in women with a uterus.

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