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OPEN

ORIGINAL STUDY

Breast effects of oral, combined 17β-estradiol, and progesterone capsules in menopausal women: a randomized controlled trial

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Abstract

Objective: To evaluate the effect of a single-capsule, bioidentical 17β-estradiol (E2) and progesterone (P4) hormone therapy on mammograms and breasts in postmenopausal women after 1 year of use.

Methods: In the 12-month, phase 3, randomized, double-blind, placebo-controlled, multicenter REPLENISH trial, postmenopausal women (40-65 y) with moderate to severe vasomotor symptoms and a uterus were randomized to four active daily dose groups of E2/P4 (TX-001HR) or a placebo group. Mammograms were performed and read locally at screening (or ≤6 months before first dose) and at study end using BI-RADS classification. Incidence of abnormal mammograms and breast adverse events was evaluated.

Results: All but 8 (0.4%) mammograms at screening were normal (BI-RADS 1 or 2). At 1 year, 39 (2.9%) of the 1,340 study-end mammograms were abnormal (BI-RADS 3 or 4); incidence was 1.7% to3.7% with active doses and 3.1% with placebo. Breast cancer incidence was 0.36% with active doses and 0% with placebo. Breast tenderness was reported at frequencies of 2.4% to 10.8% with active doses versus 0.7% with placebo, and led to eight study discontinuations (1.6% of discontinuations in active groups).

Conclusions: In this phase 3 trial of a combined E2/P4, results of secondary outcomes suggest that E2/P4 may not be associated with increased risk of abnormal mammograms versus placebo, and the incidence of breast tenderness was low relative to most of the rates reported in other studies using hormone therapy.

Key Words: Breast cancer – Combined hormone – Mammogram – Menopause – Natural progesterone – Vasomotor symptoms.

Menopausal hormone therapy (HT) is widely used to treat menopausal symptoms, with currently about 12 million users in western countries.[1] However, women have concerns in starting or continuing HT due to side effects, including adverse effects on the breast. Large observational studies on HT suggest elevated breast cancer risk with the use of combined estrogen and synthetic progestin.[2-7] Additionally, combined estrogen and synthetic progestin is associated with an increased incidence of abnormal mammograms[8,9] and increased breast density.[10-15] Abnormal mammograms often lead to additional breast procedures such as repeated mammography, ultrasound, and breast biopsies, causing distress in women and reducing their quality of life.[16-18] In addition, hormone use can adversely influence mammographic screening sensitivity and delay breast cancer diagnosis.[8,19] Some studies also showed a better risk profile for HT containing progesterone (P4) rather than synthetic progestins pertaining to risk of breast cancer,[4,5,7,20-22] mammographic breast density,[23] and breast cell proliferation in women.[24]

To fulfill the unmet need for a combined HT with 17β-estradiol (E2) and P4, four combinations of bioidentical E2/P4 were developed and studied in a large, randomized, double-blinded, phase 3 trial (REPLENISH) for efficacy and safety.[25] The formulations combine solubilized E2 and P4 in single, oral soft-gel capsule (TX-001HR) and were studied for the treatment of moderate to severe vasomotor symptoms (VMS) in postmenopausal women with a uterus. The two highest doses of

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E2/P4 (1 mg E2/100 mg P4 and 0.5 mg E2/100 mg P4) were shown to effectively reduce VMS while providing endometrial protection.[25,26] The highest dose (1 mg E2/100 mg P4) studied in REPLENISH was approved by the FDA as Bijuva ([E2 and P4] capsules; TherapeuticsMD, Boca Raton, FL) in October 2018 and is the first and only FDA-approved HT that combines bioidentical E2 and P4 within a single capsule.

This report examines the influence of 1 year of TX-001HR use on the breast, including the incidence of abnormal mammograms and breast adverse events (AEs) in the REPLENISH trial.

METHODS

Study design

The multicenter, 12-month, randomized, double-blind, placebo-controlled, phase 3 REPLENISH trial (NCT01942668) was conducted in accordance with FDA's Good Clinical Practice guidelines at 117 sites in the United States. Study materials, including the clinical protocol, protocol amendments, consent form, and recruitment materials, were approved by an institutional review board at each study site.

Enrolled participants with moderate to severe VMS were randomized 1:1:1:1:1 to five groups (oral TX-001HR doses of 1 mg E2/100 mg P4, 0.5 mg E2/100 mg P4, 0.5 mg E2/50 mg P4, or 0.25 mg E2/50 mg P4, or placebo) for 12 months in a VMS substudy using a reproducible and computer-generated block randomization schedule.[25] The remaining participants who were not in the VMS substudy were randomized 1:1:1:1 to the four active E2/P4 doses. All randomized women who took one or more doses were included in the safety population for evaluating overall drug safety. A double-dummy design was used, where the daily dose was comprised of two otherwise identical capsules with different sizes to maintain study blinding.[25] The primary efficacy endpoints of REPLENISH were mean changes in frequency and severity of moderate to severe VMSs from baseline to weeks 4 and 12 with E2/P4 versus placebo in the VMS substudy, and the primary safety endpoint was the endometrial hyperplasia incidence at month 12 with E2/P4. Additional safety endpoints included changes from baseline in breast examinations and mammograms.

Participants

Inclusion and exclusion criteria have been described previously.[25] In brief, healthy postmenopausal women aged 40-65 years, with an intact uterus, body mass index $\leq$ 34.0 kg/m^2, and seeking VMS treatment were eligible. Postmenopausal was defined as one of the following conditions: $\geq$12 months of spontaneous amenorrhea; $\geq$ 6 months of spontaneous amenorrhea with $>$ 40 mIU/mL screening serum follicle-stimulating hormone level; or $\geq$ 6 weeks after bilateral oophorectomy. Eligible women had to have a normal or nonclinically significant breast examination and a normal mammogram (BI-RADS 1 or 2) that was performed at screening or within 6 months before the first dose. Women with a BI-RADS 0 (incomplete) screening mammogram were excluded. Additional inclusion and exclusion criteria were typical for HT assessment studies, as described elsewhere.[25] Written informed consent was obtained from all participants.

Safety assessment

AEs that occurred during the study were collected through 15 days after the last dose for nonserious AEs, 30 days for serious AEs. Treatment-emergent adverse events (TEAEs) were recorded on or after the first dose through 15 days after the last dose. All TEAEs were summarized by system organ class and preferred term using MedDRA Version 18.0 (Geneva, Switzerland). When one TEAE occurred more than once for the same woman, the TEAE was counted once for each preferred term and once within each system organ class. Multiple TEAEs in one woman were listed using the maximum severity and strongest relationship. All AEs were assessed to determine the severity and relationship with the treatment, and all were followed up until a satisfactory resolution.

Breast examination was performed at the time of screening, month 6, and month 12 (end of treatment or early termination). Mammograms were performed and read locally at screening (or within 6 mo before initial treatment) and at the end of the study (month 12 or early termination). Each mammogram was assessed using the universal classification system-Breast Imaging and Reporting and Database System (BI-RADS) (Table 1),[27] and given a BI-RADS score. Women with mammograms of BI-RADS 1 (negative) and BI-RADS 2 (benign) at screening were eligible for enrollment. Mammograms with BI-RADS 3 (probably benign) and BI-RADS 4 (suspicious for malignancy) were considered abnormal, and with incomplete mammograms (BI-RADS 0), were not acceptable for enrollment.

TABLE 1. *BI-RADS score description and management recommendations*[27]

BI-RADS Score	Description	Management recommendations
0	Incomplete	May require additional imaging
1	Negative	Routine screening recommended
2	Benign	Routine screening recommended
3	Probably benign	Short-term (6-mo) follow-up or continued surveillance
4	Suspicious for malignancy	Tissue diagnosis
5	Highly suggestive of malignancy	Tissue diagnosis
6	Known biopsy-proven malignancy	Surgical excision when clinically appropriate

BI-RADS, breast imaging and reporting and database system.

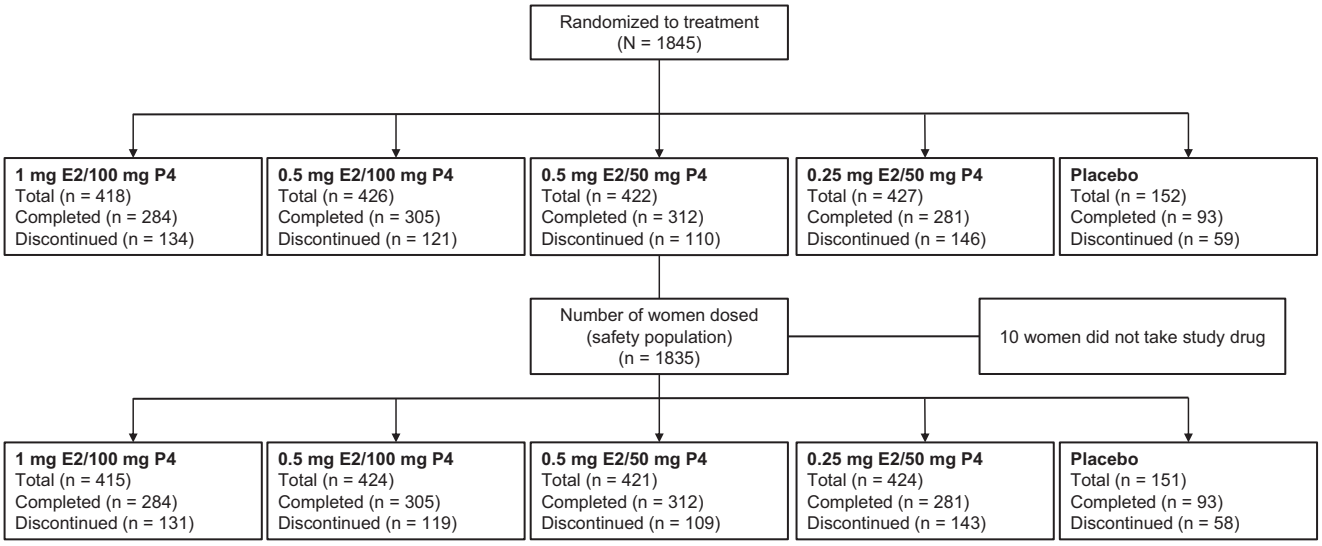

FIG. 1. Disposition of the safety population in the REPLENISH study. E2, 17β-estradiol; P4, progesterone.

Statistical analysis

The overall study sample size was determined based on the primary safety and efficacy endpoints as previously described.[25] A post hoc power determination was made on the sample of women with mammogram data. With approximately 100 women in the placebo group and 300 women in an active treatment group, the study had an estimated power of 74% to detect a difference of threefold increase (eg from 3% with placebo to 12% with an active dose) in the incidence of abnormal mammogram (BI-RADS 3 or 4). Baseline and demographic characteristics were descriptively summarized by treatment group. Incidence of AEs was calculated with the number of women in the safety population as the denominator ($n = 1{,}835$). Incidence of abnormal mammograms was calculated using the number of women with specific mammogram findings (eg, BI-RAD 1/2 or 3/4) as the numerator and the number of women with available mammograms as the denominator. For women who had more than one follow-up mammogram, only the last one was included as the study-end mammogram. Analysis was performed using SAS v.9.2 (SAS Institute, Cary, NC).

RESULTS

Participant disposition and demographics

Of the 1,845 women randomized in the study, 1,835 received at least one dose of the study drug and formed the safety population (Fig. 1). In the safety population, 1,275 women (69.5%) completed the 52-week treatment. The most common reasons for discontinuation from the study included AEs (9.1% and 6.6% with E2/P4 and placebo, respectively), withdrawal of consent (8.2% and 8.6%), lack of efficacy (1.4% and 7.9%), and lost to follow-up (7.2% and 11.3%).

Overall, demographic and baseline characteristics were comparable between groups in the safety population (Table 2). The population in which study-end mammograms were performed included 1,340 women. Demographics were similar to those of the overall safety population (Table 2).

TABLE 2. *Demographic and baseline characteristics in safety population*

Characteristic	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	Total
n	415	424	421	424	151	1,835
Age (y)						
Mean ± SD	54.7 ± 4.4	54.5 ± 4.5	54.9 ± 4.3	54.4 ± 4.0	54.5 ± 4.3	54.6 ± 4.3
Ethnic origin, *n* (%)						
White	271 (65.3)	281 (66.3)	276 (65.6)	273 (64.4)	100 (66.2)	1,201 (65.4)
AfricanAmerican	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)
Time since menopause, y						
Mean ± SD	5.8 ± 4.9	6.0 ± 5.1	5.7 ± 4.6	5.6 ± 4.9	6.0 ± 5.3	5.8 ± 4.9
Bilateral oophorectomy, *n* (%)	4 (1.0)	6 (1.4)	3 (0.7)	3 (0.7)	0	16 (0.9)
n	415	424	421	423	151	1,834
BMI (kg/m^2)						
Mean ± SD	26.8 ± 4.1	26.7 ± 4.3	26.7 ± 4.0	26.7 ± 4.0	26.6 ± 3.9	26.7 ± 4.1

BMI, body mass index; E2, 17β-estradiol; P4, progesterone; SD, standard deviation.
[a]Other includes: Other (20), Asian (12), American Indian or Alaska Native (6), Native Hawaiian or Pacific Islander (5), and Unknown (2).

TABLE 3. *BI-RADS classification of mammograms at screening and at study end*

BI-RADS, *n/N* (%)[a]	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
Screening					
0 (Incomplete)	0/415 (0.0)	0/422 (0.0)	1/421 (0.2)	1/422 (0.2)	0/151 (0.0)
[95% CI]	[0.0-0.9]	[0.0-0.9]	[0.0-1.3]	[0.0-1.3]	[0.0-2.4]
1/2 (Normal)	414/415 (99.8)	422/422 (100.0)	417/421 (99.1)	418/422 (99.1)	150/151 (99.3)
[95% CI]	[98.7-100.0]	[99.3-100.0]	[97.6-99.7]	[97.6-99.7]	[96.4-100.0]
3/4 (Abnormal)	1/415 (0.2)	0/422 (0.0)	3/421 (0.7)	3/422 (0.7)	1/151 (0.7)
[95% CI]	[0.0-1.3]	[0.0-0.9]	[0.2-2.1]	[0.2-2.1]	[0.0-3.6]
P value[b]	0.4627	0.2635	>0.9999	>0.9999	
Study end					
0 (Incomplete)	2/300 (0.7)	2/314 (0.6)	1/325 (0.3)	4/303 (1.3)	0/98 (0.0)
[95% CI]	[0.1-2.4]	[0.1-2.3]	[0.0-1.7]	[0.4-3.4]	[0.0-3.7]
1/2 (Normal)	287/300 (95.7)	301/314 (95.9)	315/325 (96.9)	294/303 (97.0)	95/98 (96.9)
[95% CI]	[92.7-97.7]	[93.0-97.8]	[94.4-98.5]	[94.4-98.6]	[91.3-99.4]
3/4 (Abnormal)	11/300 (3.7)	11/314 (3.5)	9/325 (2.8)	5/303 (1.7)	3/98 (3.1)
[95% CI]	[1.8-6.5]	[1.8-6.2]	[1.3-5.2]	[0.5-3.8]	[0.6-8.7]
P value[b]	>0.9999	>0.9999	>0.9999	0.4105	

BI-RADS, breast imaging and reporting and database system; CI, confidence interval; E2, 17β-estradiol; P4, progesterone.
[a]Percentage was calculated using number of women with available mammograms as the denominator.
[b]*P* value was calculated for active dose versus placebo.

Abnormal mammograms

Mammograms were performed and read locally for 1,831 women at screening and 1,340 women at study end (Month 12 or early termination) (Table 3).

The majority (99.5%) of the screening mammograms were normal (BI-RADS 1 or 2). Two women had a BI-RADS score of 4 at screening, but were included since no evidence of malignancy was observed before randomization. After up to 1 year of treatment, most (96.4%, $n = 1,292$) of the 1,340 study-end mammograms were normal (BI-RADS 1 or 2). Only a small portion (2.9%, $n = 39$) were abnormal (BI-RADS 3 or 4) and nine (0.7%) were incomplete (BI-RADS 0) (Table 3). Comparable rates of abnormal mammograms were observed in all the study groups (Fig. 2), ranging from 1.7% to 3.7% with E2/P4 doses, and 3.1% with placebo.

Breast cancer

Of the 1,684 women who were randomized to receive E2/P4, six (0.36%) women were diagnosed with invasive breast cancer during the study (Table 4); five of them completed the 52-week treatment and one discontinued due to the breast cancer. Two women in the 1 mg E2/100 mg P4 group were diagnosed with breast cancer, two in the 0.5 mg E2/100 mg P4 group, one in the 0.5 mg E2/50 mg P4 group, one in the 0.25 mg E2/50 mg P4 group. All had a BI-RADS 4 at the end of the study, except for one woman in the 1 mg E2/100 mg P4 group with a BI-RADS 0. None of the women in the placebo group reported breast cancer.

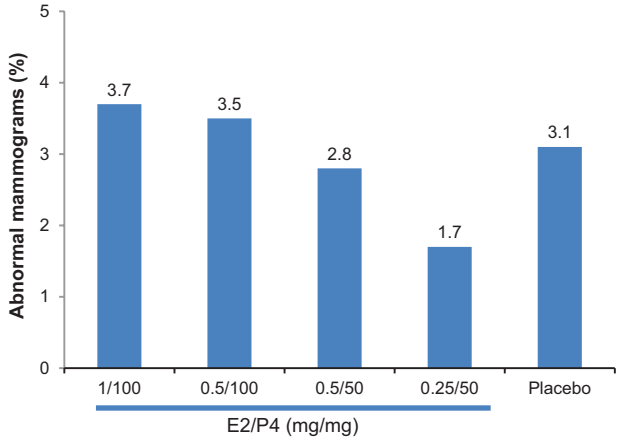

FIG. 2. Incidence of abnormal mammograms at study end. E2, 17β-estradiol; P4, progesterone.

Breast tenderness, pain, and swelling

TEAEs of breast tenderness were reported in all groups of the safety population. The incidence ranged from 2.4% to 10.8% across the four active doses, versus 0.7% with placebo (Table 4). Most of these breast tenderness AEs were mild (75%) or moderate (23%); and more than half (52%) occurred in the first 28 days of treatment with most of those being self-resolving (77%). In the active treatment groups, 1.3% of women had TEAEs coded as breast pain, discomfort, or swelling (Table 4), all of which were mild or moderate. Of the 502 women who discontinued E2/P4, only eight (1.6%) had breast tenderness as the primary reason for withdrawal (Table 5).

DISCUSSION

In the REPLENISH trial, a low incidence (1.7% to 3.7%) of abnormal mammograms was observed with all E2/P4 doses after up to 1 year of use, similar to that with placebo (3.1%). Given the overlapping 95% CIs and the fact that incidence with placebo was higher than with the two lower E2/P4 doses, the between-group abnormal mammogram incidence can be considered similar between groups. These mammogram results are in contrast to the previous Women's Health Initiative (WHI) arm of conjugated equine estrogens plus medroxyprogesterone acetate in which a substantially higher incidence of abnormal mammograms was reported in women who used combined HT than those who took placebo for

TABLE 4. *Incidence of breast-related adverse events of interest*

	1 mg E2/100 mg P4 ($n = 415$)	0.5 mg E2/100 mg P4 ($n = 424$)	0.5 mg E2/50 mg P4 ($n = 421$)	0.25 mg E2/50 mg P4 ($n = 424$)	Placebo ($n = 151$)
AEs, *n* (%)					
Breast cancer[a]	2 (0.5)	2 (0.5)	1 (0.2)	1 (0.2)	0 (0.0)
[95% CI]	[0.1-1.7]	[0.1-1.7]	[0.0-1.3]	[0.0-1.3]	[0.0-2.4]
P value[b]	>0.9999	>0.9999	>0.9999	>0.9999	
Benign breast neoplasm	4 (1.0)	5 (1.2)	4 (1.0)	3 (0.7)	1 (0.7)
[95% CI]	[0.3-2.4]	[0.4-2.7]	[0.3-2.4]	[0.1-2.1]	[0.0-3.6]
P-value[b]	>0.9999	>0.9999	>0.9999	>0.9999	
Breast calcifications	3 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
[95% CI]	[0.1-2.1]	[0.0-0.9]	[0.0-0.9]	[0.0-1.3]	[0.0-2.4]
P value[b]	0.5685			>0.9999	
Breast cyst	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
[95% CI]	[0.0-1.3]	[0.0-0.9]	[0.0-0.9]	[0.0-0.9]	[0.0-2.4]
P value[b]	>0.9999				
Breast mass	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
[95% CI]	[0.0-0.9]	[0.0-1.3]	[0.0-0.9]	[0.0-0.9]	[0.0-2.4]
P value[b]		>0.9999			
TEAEs, *n* (%)					
Breast tenderness	45 (10.8)	19 (4.5)	25 (5.9)	10 (2.4)	1 (0.7)
[95% CI]	[8.0-14.2]	[2.7-6.9]	[3.9-8.6]	[1.1-4.3]	[0.0-3.6]
P-value[b]	<0.0001	0.0348	0.0052	0.3035	
Breast pain	9 (2.2)	2 (0.5)	1 (0.2)	2 (0.5)	0 (0.0)
[95% CI]	[1.0-4.1]	[0.1-1.7]	[0.0-1.3]	[0.1-1.7]	[0.0-2.4]
P-value[b]	0.1215	>0.9999	>0.9999	>0.9999	
Breast discomfort	3 (0.7)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
[95% CI]	[0.1-2.1]	[0.0-1.3]	[0.0-0.9]	[0.0-0.9]	[0.0-2.4]
P value[b]	0.5685	>0.9999			
Breast swelling	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)
[95% CI]	[0.1-1.7]	[0.0-0.9]	[0.1-1.7]	[0.0-0.9]	[0.0-2.4]
P value[b]	>0.9999		>0.9999		

AE, adverse event; TEAE, treatment-emergent adverse event; E2, 17β-estradiol; P4, progesterone.
[a]Breast cancer includes invasive ductal breast carcinoma.
[b]*P* value was calculated for active dose versus placebo.

1 year (9.4% vs 5.4%; $P < 0.001$).[8,19] Additionally, the previously observed background incidence of abnormal results in screening mammograms in the US was reported as 6.0% (BI-RADS 3) and 2.1% (BI-RADS 4,5).[28]

Our analysis showed an incidence (0.36%) of breast cancer in women who used E2/P4, whereas 0% in those with placebo. The rate with E2/P4 is comparable to the 0.33% (annualized percentage) incidence of invasive breast cancer reported for the placebo group in the WHI study,[8] as well as that observed with placebo in the postmenopausal estrogen/progestin interventions trial (0.6%).[29] The surveillance, epidemiology, and end results data showed that the background breast cancer incidence in women between ages of 40 and 64 years was approximately 0.3%.[30] Although the participants in REPLENISH were relatively healthier than the general population, which is typical in registrational studies of HT, the small number of breast cancer cases with E2/P4 suggests potentially no detrimental effect on breast cancer risk in this short study duration. The incidence of benign breast neoplasm with E2/P4 was also relatively low (0.7% to1.2%), similar to that with placebo (0.7%). Although P4 and synthetic progestins bind to the P4 receptor in breast tissue, there is preclinical evidence that each type of progestogen has a unique effect on the breast. Large European observational studies show a differential effect of HT containing progestins or P4 on breast cancer risk. An increase in breast cancer risk was found in women taking estrogen with synthetic progestogens but not estrogens with P4 (Table 6) in the E3N ($n = 54,548$) and E3N-EPIC ($n = 80,377$) cohorts.[4-6] A French case-control study ($n = 1,232$) also found that estrogen plus P4 did not increase breast cancer risk, whereas estrogen plus synthetic progestogens significantly elevated the risk, especially testosterone-derived progestogens (nortestosterones)

TABLE 5. *Breast adverse events leading to study withdrawal*

	1 mg E2/100 mg P4 ($n = 415$)	0.5 mg E2/100 mg P4 ($n = 424$)	0.5 mg E2/50 mg P4 ($n = 421$)	0.25 mg E2/50 mg P4 ($n = 424$)	Placebo ($n = 151$)
Total withdrawal	131 (31.6)	119 (28.1)	109 (25.9)	143 (33.7)	58 (38.4)
Breast AE to withdraw					
Breast cancer	1 (0.2)	0	0	0	0
Breast tenderness	6 (1.4)	0	2 (0.5)	0	0
Breast pain	0	1 (0.2)	0	1 (0.2)	0
Breast swelling	1 (0.2)	0	0	0	0

AE, adverse event; E2, 17β-estradiol; P4, progesterone .

TABLE 6. *Risk of breast cancer with hormone therapy containing progesterone or progestins in large observational studies*

Study	Estrogen and/or progestogen	HR (95% CI)
Fournier et al, 2014[6]	Estrogen alone	1.17 (0.99-1.38)
	Estrogen plus progesterone/dydrogesterone	1.22 (1.11-1.35)
	Estrogen plus synthetic progestins	1.87 (1.71-2.04)
Cordina-Duverger et al, 2013[7]	Estrogen alone (any)	1.19 (0.69-2.04)
	Estrogen (any) with progestogens	1.33 (0.92-1.92)
	Natural progesterone	0.80 (0.44-1.43)
	Synthetic progestins	1.72 (1.11-2.65)
	Progesterone derivatives	1.57 (0.99-2.49)
	Testosterone derivatives	3.35 (1.07-10.4)
Fournier et al, 2008[5]	Oral estrogen alone	1.32 (0.76-2.29)
	Oral estrogen plus progestogen	
	Progesterone	Not analyzed[a]
	Dydrogesterone	0.77 (0.36-1.62)
	Medrogestone	2.74 (1.42-5.29)
	Chlormadinone acetate	2.02 (1.00-4.06)
	Cyproterone acetate	2.57 (1.81-3.65)
	Promegestone	1.62 (0.94-2.82)
	Nomegestrol acetate	1.10 (0.55-2.21)
	Norethisterone acetate	2.11 (1.56-2.86)
	Medroxyprogesterone acetate	1.48 (1.02-2.16)
	Transdermal estrogen alone	1.28 (0.98-1.69)
	Transdermal estrogen plus progestogen	
	Progesterone	1.08 (0.89-1.31)
	Dydrogesterone	1.18 (0.95-1.48)
	Medrogestone	2.03 (1.39-2.97)
	Chlormadinone acetate	1.48 (1.05-2.09)
	Cyproterone acetate	Not analyzed[a]
	Promegestone	1.52 (1.19-1.96)
	Nomegestrol acetate	1.60 (1.28-2.01)
	Norethisterone acetate	Not analyzed[a]
	Medroxyprogesterone acetate	Not analyzed[a]
Fournier et al, 2005[4]	Estrogen alone	1.1 (0.8-1.6)
	Estrogen plus progesterone	0.9 (0.7-1.2)
	Transdermal estrogen	0.9 (0.7-1.2)
	Oral estrogen	No events
	Estrogen plus synthetic progestins	1.4 (1.2-1.7)
	Transdermal estrogen	1.4 (1.2-1.7)
	Oral estrogen	1.5 (1.1-1.9)

Adapted from *Mirkin (2018)*[45] with permission from Taylor & Francis Ltd.
CI, confidence interval; HR, hazard ratio.
[a]Not analyzed, <5 breast cancer cases.

(Table 6).[7] Systematic reviews and meta-analyses also found results consistent with these large observational studies.[20,21,31] Increased breast cancer risk was found in the most recent E3N analysis with current use of estrogen plus synthetic progestogens for ≤5 years and >5 years (with a greater magnitude than with P4).[6] In the analyses, P4 and dydrogesterone were combined and therefore definitive conclusions about long-term (>5 y) P4 use are not possible.[6]

Breast discomfort, such as breast tenderness or breast pain, is a common side effect associated with HT and often causes women to quit therapy. New-onset breast tenderness after initiation of combined HT was found to be linked with increased mammographic density and elevated breast cancer risk.[15,32-34] The prevalence of moderate to severe breast tenderness in the WHI was 9.3% with estrogen plus progestin,[35] and the rate increased to 36% when breast tenderness AEs of all severity were included,[33] a rate significantly higher than that with placebo. Similar high incidence of breast tenderness or breast pain was also observed in other randomized controlled studies, ranging from 13% to 26%.[15,36,37] In the REPLENISH study, breast tenderness of all severity occurred at a rate of 2.4% to10.8% in women who received E2/P4, less frequently than most of the rates reported for estrogen plus progestin in previous studies.[15,32-34,36,37] Although the highest incidence (10.8%) was with the highest dose of 1 mg E2/100 mg P4, the rate with 0.5 mg E2/100 mg P4 (4.5%) was slightly lower than that with 0.5 mg E2/50 mg P4 (5.9%), and their 95% CIs overlapped considerably, showing no clear dose dependence. Moreover, 1.6% of the women who discontinued E2/P4 reported breast tenderness as the primary reason to withdraw. This is much lower than the 13% reported in the Women's International Study of long Duration Oestrogen after Menopause,[37] suggesting the influence of TX-001HR on the breast was tolerable in most of the women in this study. The overall impact of TX-001HR on the breast is consistent with previous findings that combined HT containing natural P4 is associated with little or no increase in breast cancer risk and a lower incidence of breast tenderness than that with synthetic progestogen.[4,5,7,38]

One limitation of the study is that analysis of breast density changes with E2/P4 was not a prespecified endpoint in the REPLENISH study. Increased breast density is often found in

women using HT containing a progestin.[10-15] Greater breast density may be associated with increased breast cancer risk,[10,14,39,40] although it is unknown whether the elevated breast cancer risk by combined HT is mediated through hormone-induced breast density change.[41] Another limitation of the study is the relative short duration time for observations of breast changes. As a longer duration of combined hormone use is associated with higher breast cancer risk,[1] our study is likely not sufficiently powered to observe long-term breast safety of TX-001HR (in addition to the low incidence of breast cancer in women of similar age). Nevertheless, this duration is typical in evaluating menopausal hormone medications and the study suggests short-term breast safety of TX-001HR.

The REPLENISH trial demonstrated significant reduction in the severity and frequency of VMS with the two highest doses of TX-001HR studied[25] with favorable safety profiles including endometrial protection,[25] pharmacologically effective absorption,[26] improved quality of life, and sleep outcomes,[42,43] and no adverse effects on cardiometabolic markers.[44] The results reported here suggest that the TX-001HR, an FDA-approved bioidentical combined HT is potentially safe with no significant adverse impact on the breast after 1 year of use.

CONCLUSIONS

In the large, randomized, controlled, phase 3 REPLENISH study of TX-001HR, in which combined E2/P4 oral formulations were studied for menopausal moderate to severe VMS treatment, the incidence of abnormal mammograms with E2/P4 was low and comparable to that with placebo. Breast cancer occurred in a small percentage of women who used E2/P4. The results from the present analysis showed that the study drug was not associated with increased risk of abnormal mammograms after 1 year of use and caused relatively less breast discomfort compared with those reported in studies of other HT formulations.

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