E2/P4 Capsules Reduced Vasomotor Symptoms Irrespective of Age and BMI in the REPLENISH Trial

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Introduction

- Vasomotor symptoms (VMS), which include hot flushes and sweating, are consistently associated with transitions through menopausal stages, and experienced by at least 50% of menopausal women[1]
  - In the SWAN study, the median duration of VMS was 7.4 years[2]
- Administration of estrogen or estrogen/progestogen therapy to postmenopausal women significantly improves menopausal symptoms
- REPLENISH was a phase 3 trial that evaluated the safety and efficacy of four daily doses of bioidentical 17β-estradiol and progesterone (E2/P4; previously known as TX-001HR) for treating moderate to severe VMS in menopausal women with a uterus
  - Doses of E2/P4 (mg/mg) 1/100 and 0.5/100 significantly improved frequency and severity of moderate to severe hot flushes at weeks 4 and 12 from baseline vs placebo (all co-primary endpoints met)[3]
  - The 1/100 dose was approved last year as Bijuva® (TherapeuticsMD, Boca Raton, FL)

Objective

To evaluate the efficacy of E2/P4 for treating moderate to severe vasomotor symptoms in postmenopausal women by age and body mass index (BMI)

Methods

- REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial of healthy postmenopausal women (age 40 to 65 years) with a uterus seeking treatment for moderate to severe VMS
- Women experiencing ≥7/day (or ≥50 per week) moderate to severe hot flushes were randomized to one of four E2/P4 doses (1/100, 0.5/100, 0.5/50, 0.25/50) or placebo (VMS substudy), while those with less severe VMS were randomized to active treatments only
- Co-primary efficacy endpoints of the VMS substudy were changes in frequency and severity of VMS with E2/P4 vs placebo at weeks 4 and 12
- Percent changes in the weekly frequency and severity of moderate to severe VMS from baseline at weeks 4 and 12 vs placebo were analyzed in the VMS substudy according to:
  - Age: <55 and ≥55 years
  - BMI: <25 kg/m^2, 25 to <30 kg/m^2, or ≥30 kg/m^2

Results

Participant Demographics and Subgroup Characteristics

- Women in the VMS substudy had a mean age of 54.7 years (range, 40–65 years) and a mean BMI of 26.6 kg/m^2 (range, 14.0–34.5 kg/m^2)
- Approximately half the women were <55 years old and most (77.2%) had a BMI <30 kg/m^2 (**Table 1**)

Table 1. Study participant age and BMI subgroup distribution

Parameter	n (%)	Parameter	n (%)
Age, y		**BMI, kg/m^2**	
<55	367 (50.6)	<25	259 (35.7)
≥55	359 (49.4)	25 to <30	301 (41.5)
		≥30	166 (22.8)

- Baseline frequency and severity of moderate to severe VMS were numerically higher in the <55 age group than in the ≥55 group; BMI baseline values varied across subgroups for VMS frequency (**Table 2**)

Table 2. Baseline scores for frequency and severity of moderate to severe VMS by age and BMI

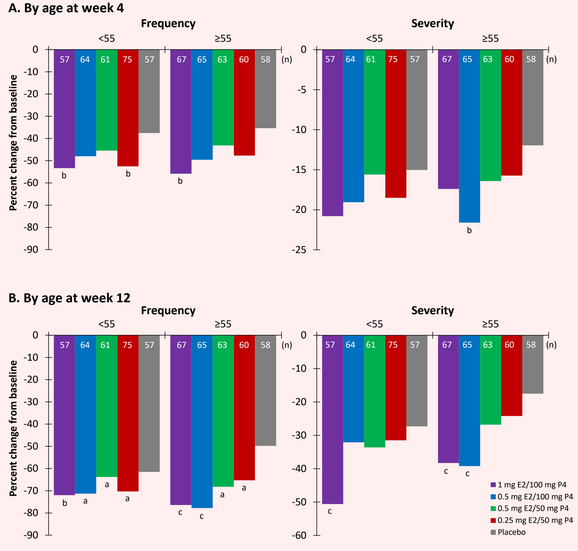
Subgroup	Estradiol/Progesterone (mg/mg)								Placebo	
	1/100		0.5/100		0.5/50		0.25/50			
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Frequency										
Age, y										
<55	68	78.7±43.9	74	71.7±29.4	69	77.9±33.1	86	79.4±34.6	70	72.7±24.8
≥55	73	70.4±24.4	75	72.4±26.2	78	74.2±22.7	68	74.0±24.1	65	72.1±21.6
BMI, kg/m^2										
<25	54	80.4±45.4	49	69.0±21.4	52	75.9±23.3	58	82.4±35.3	46	73.0±20.8
25 to <30	56	73.5±23.1	55	70.3±30.3	64	76.5±30.8	65	72.0±26.2	61	70.5±25.4
≥30	31	65.6±32.3	45	77.6±30.3	31	74.6±30.3	31	77.5±27.9	28	75.7±22.7
Severity										
Age, y										
<55	68	2.55±0.37	74	2.52±0.21	69	2.50±0.22	86	2.54±0.25	70	2.53±0.24
≥55	73	2.53±0.27	75	2.50±0.29	78	2.50±0.24	68	2.48±0.27	65	2.51±0.26
BMI, kg/m^2										
<25	54	2.53±0.25	49	2.53±0.27	52	2.49±0.23	58	2.59±0.28	46	2.48±0.27
25 to <30	56	2.61±0.24	55	2.46±0.25	64	2.48±0.23	65	2.43±0.21	61	2.54±0.24
≥30	31	2.44±0.50	45	2.56±0.21	31	2.56±0.24	31	2.54±0.27	28	2.55±0.23

Efficacy of E2/P4 for Treating VMS by Age and BMI

By Age

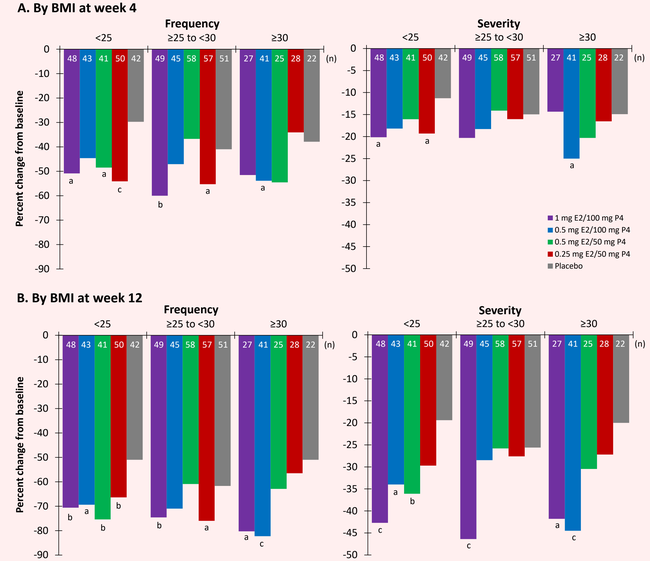
- Percent changes from baseline in frequency with E2/P4 were similar between age groups at weeks 4 (43%–56%; **Figure 1A**) and 12 (64%–78%; **Figure 1B**)
- Even though subgroup analyses were not powered for statistical significance, significant percent change reductions in VMS frequency were observed for all age subgroups with 1/100 and for most with the 0.5/100 groups vs placebo at week 12 (**Figure 1B**); fewer significant differences were observed at week 4 (**Figure 1A**)
- Percent changes from baseline with E2/P4 for severity ranged from 16%–22% at week 4 and 24%–51% for either age group at week 12 (**Figure 1AB**)

Figure 1. Mean percent change from baseline to week 12 in weekly frequency of VMS by age



[a]*P*<0.05; [b]*P*<0.01; [c]*P*≤0.001 vs placebo for mean change from baseline.

Figure 2. Mean percent change from baseline to week 12 in weekly severity of VMS by BMI



[a]*P*<0.05; [b]*P*<0.01; [c]*P*≤0.001 vs placebo for mean change from baseline.

By BMI

- Percent changes from baseline in severity with E2/P4 were similar between BMI groups at week 4 (14%–25%) and week 12 (27%–46%)
- Larger percent reductions in VMS frequency and severity were observed with E2/P4 vs placebo, with some BMI subgroups meeting statistical significance at weeks 4 and 12 depending on dose (**Figure 2AB**)
  - Most of the BMI subgroups had significant reductions in severity and frequency with the 1/100 and 0.5/100 doses, with more significant differences at week 12 than week 4

Conclusions

- While the study was not powered to detect statistical significance when analyzed by subgroup, the two highest oral E2/P4 doses (1/100 and 0.5/100) reduced VMS frequency and severity, regardless of age or BMI
- These subgroup analyses demonstrate a consistency of effect of E2/P4 among different age and BMI populations

Disclosures

- DB is on the speaker's bureau for TherapeuticsMD. RCB is on the speaker's bureau for TherapeuticsMD. SG, BB, and SM are employees of TherapeuticsMD with stock/stock options. BB is also a Board member of TherapeuticsMD.
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References

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