Effects of Single-Capsule 17β-Estradiol/Progesterone (TX-001HR) on Weight and Blood Pressure in Postmenopausal Women of the REPLENISH Trial

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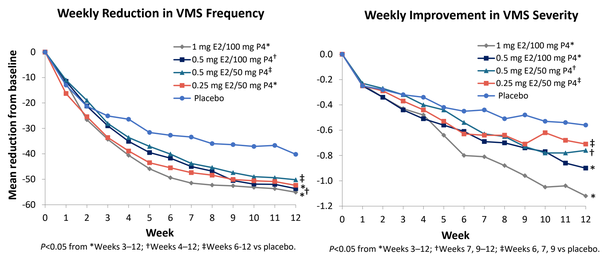
Introduction

- Body weight and central adipose distribution are known to increase during and after the menopausal transition[1,2]
- High blood pressure (BP) becomes more prevalent in women after menopause, and is one of the major risk factors for cardiovascular morbidity and mortality in postmenopausal women[3,4]
- Reviews of clinical studies generally show a neutral to beneficial effect of menopausal hormone therapy on body weight and weight distribution[1,2] and blood pressure[5,6] during menopause; although, cardiovascular risks with hormone therapy remain controversial
- An investigational combination of 17β-estradiol and progesterone (E2/P4; TX-001HR) in a single, oral softgel capsule was shown at most doses to significantly reduce the frequency and severity of vasomotor symptoms (VMS) in postmenopausal women in the REPLENISH trial (**Figure 1**)[7]

Figure 1. Weekly Reduction in VMS frequency and Severity in the REPLENISH Trial



P<0.05 from *Weeks 3–12; †Weeks 4–12; ‡Weeks 6-12 vs placebo. *P*<0.05 from *Weeks 3–12; †Weeks 7, 9–12; ‡Weeks 6, 7, 9 vs placebo.

Objective

To examine the effects of E2/P4 on body weight and BP in postmenopausal women of the REPLENISH trial

Methods

- REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that evaluated TX-001HR for relief of moderate to severe VMS in postmenopausal women with a uterus
- Women with menopausal VMS, aged 40 to 65 years with body mass index (BMI) ≤34 kg/m^2 and BP ≤140/90 mm Hg and a uterus, were eligible to participate
- Women with moderate to severe hot flushes (≥7/day or ≥50/week) were enrolled in a VMS substudy and randomized to daily E2/P4 (mg/mg) 1/100, 0.5/100, 0.5/50, 0.25/50 or placebo; women who did not qualify for the VMS substudy (with less severe or less frequent VMS) were randomized to E2/P4 doses only for endometrial assessment (reported elsewhere) in the general study, which also assessed overall safety[7]
  - Ratio of women receiving E2/P4 to placebo was approximately 11 to 1
  - Safety population included all women who were randomized and took ≥1 capsule of E2/P4
- As part of overall safety, body weight and sitting BP were assessed at baseline, weeks 4, 8 and 12, and months 6, 9 and 12; changes from baseline to month 12 for these endpoints were summarized using descriptive statistics
- Potentially clinically important (PCI) changes were defined as increases or decreases from baseline as follows:
  - Weight: ≥15% and ≥11.3 kg (25 lbs)
  - Systolic BP: ≥20 mm Hg, with absolute value ≥160 or ≤90 mm Hg
  - Diastolic BP: ≥15 mm Hg, with absolute value ≥90 or ≤60 mm Hg

Results

Disposition and Demographics

- The safety population included 1835 women who took E2/P4 of 1 mg/100 mg (n=415), 0.5 mg/100 mg (n=424), 0.5 mg/50 mg (n=421), 0.25 mg/50 mg (n=424), or placebo (n=151)
  - Discontinuation rates due to weight gain (E2/P4: 0.2-0.9%; placebo: 0.7%) or hypertension (E2/P4: 0-0.5%; placebo: 0.7%) were low
- Patients had a mean age of 55 years, mean BMI of 27 kg/m^2, and mean weight of 72 kg; 65% were white and 32% were African American (**Table 1**)

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

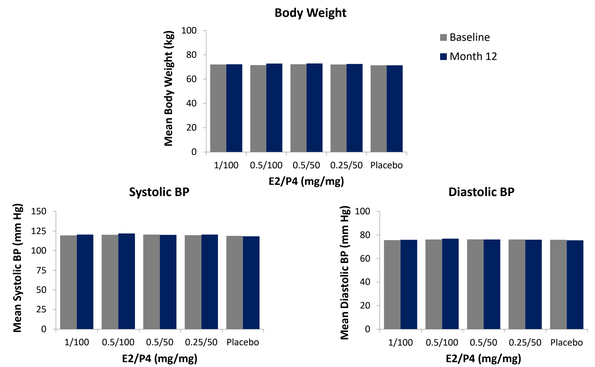
Characteristic	Estradiol/Progesterone				Placebo
	1 mg/ 100mg	0.5 mg/ 100 mg	0.5 mg/ 50 mg	0.25 mg/ 50 mg	
n	415	424	421	424	151
Age, y	54.7 ± 4.4	54.5 ± 4.5	54.9 ± 4.3	54.4 ± 4.0	54.5 ± 4.3
Race, n (%)					
White	271 (65.3)	281 (66.3)	276 (65.6)	273 (64.4)	100 (66.2)
African American	134 (32.3)	136 (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 ± 4.0	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
Baseline values					
Weight, kg	72.1 ± 12.3	71.6 ± 13.1	72.2 ± 11.8	72.1 ± 11.9	71.4 ± 11.5
Systolic BP, mm Hg	119.5 ± 12.0	120.3 ± 11.7	120.5 ± 11.9	119.8 ± 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

Data shown as mean ± SD, unless stated otherwise.

Body Weight and Blood Pressure Safety Outcomes

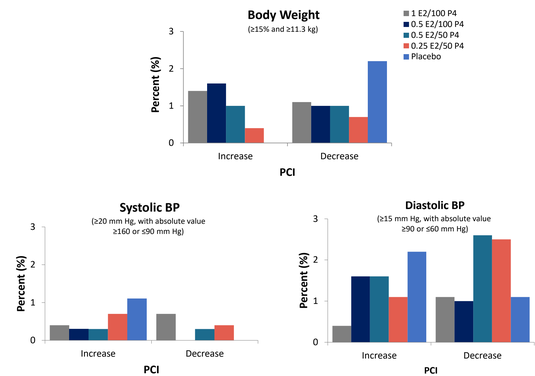
- No clinically meaningful differences or trends in the mean changes from baseline to month 12 were observed in body weight, or in systolic or diastolic BP (**Figure 2**)

Figure 2. Mean Values for Body Weight and Diastolic and Systolic BP at Baseline and Month 12



- Potentially clinically important changes from baseline to month 12 were observed in 26 (1.4%) women for weight change, 10 (0.5%) for systolic BP change and 38 (2.1%) for diastolic BP (**Figure 3**)

Figure 3. Percentages of Women with PCI Changes from Baseline to Month 12



- Weight gain and hypertension were reported as a treatment-related, treatment-emergent adverse event in few women (**Table 2**)
  - One subject (0.5 mg E2/100 mg P4) had both PCI weight gain and BP increase

Table 2. Incidence of Treatment-related, Treatment-emergent Adverse Events

	Estradiol/Progesterone				Placebo
	1 mg/ 100mg	0.5 mg/ 100 mg	0.5 mg/ 50 mg	0.25 mg/ 50 mg	
Weight gain	7 (1.7)	6 (1.4)	7 (1.7)	11 (2.6)	2 (1.3)
Hypertension*	2 (0.4)	5 (1.2)	2 (0.5)	1 (0.2)	0

*Includes categories of BP abnormal, BP diastolic increased, BP increased, BP systolic increased.

Conclusions

- Vital sign data, from the phase 3 REPLENISH trial, showed minimal, clinically insignificant changes in body weight or BP in all groups including placebo
  - These data extend the previously reported overall safety results of REPLENISH trial showing no clinically significant differences in adverse events versus placebo[7]
- TX-001HR, if approved, may be a new oral E2/P4 option for the treatment of moderate to severe VMS in postmenopausal women with a uterus

References

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Disclosures

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