Predictors of Vaginal/Uterine Bleeding with Oral TX-001HR (Estradiol and Progesterone) Capsules Taken for Menopausal Vasomotor Symptoms

Ginger Constantine, MD[1]; Steven R Goldstein, MD[2]; James H Pickar, MD[3]; Shelli Graham, PhD[4]; Brian Bernick, MD[4]; Sebastian Mirkin, MD[4]

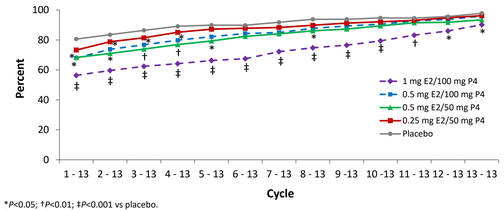
[1]EndoRheum Consultants, LLC, Malvern, PA; [2]New York University School of Medicine, New York, NY; [3]Columbia University Medical Center, New York, NY; [4]TherapeuticsMD, Boca Raton, FL

Introduction

- Vaginal bleeding associated with hormone therapy (HT) is one of the most common reasons for treatment discontinuation
- Cumulative amenorrhea rates (no bleeding or spotting for 13 cycles) range from 9% to 70% with current HT options[1-5]
- In October 2018, the US Food and Drug Administration (FDA) approved the first bioidentical HT combining 17β-estradiol and progesterone (E2/P4; 1 mg/100 mg) as Bijuva™ (TherapeuticsMD, Boca Raton, FL) in a single, oral softgel capsule for the treatment of menopausal, moderate to severe vasomotor symptoms (VMS) in women with a uterus
- The efficacy and safety of four E2/P4 doses were evaluated in the REPLENISH trial (NCT01942668) and results have been published[6]
  - Proportions of women with amenorrhea (56%-73%) and no bleeding (74%-90%) were high with up to 1 year of treatment and both were ≥90% by cycle 13 (**Figure 1**)

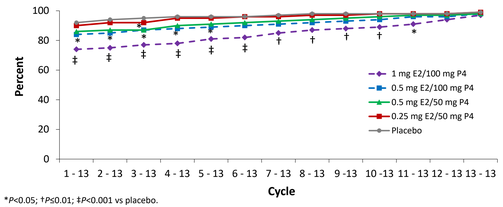
Figure 1. Cumulative (A) amenorrhea (no bleeding or spotting) and (B) no bleeding from cycle 1-13 in the safety population

A. Cumulative amenorrhea



*P<0.05; †P<0.01; ‡P<0.001 vs placebo.
Cycles are 28 days in length

B. Cumulative no bleeding



*P<0.05; †P≤0.01; ‡P<0.001 vs placebo.
Cycles are 28 days in length

Objective

To determine predictors of vaginal bleeding with E2/P4 in postmenopausal women of the REPLENISH trial

Methods

Study Design

- REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that evaluated four E2/P4 doses in postmenopausal women with a uterus[6]
- Women with moderate to severe hot flushes (≥7/day or ≥50/week) were included in a VMS substudy and were randomized 1:1:1:1:1 to daily E2/P4 (mg/mg) of 1/100, 0.5/100, 0.5/50, or 0.25/50, or placebo for 12 months; women not meeting VMS substudy eligibility were randomized 1:1:1:1 to the same active E2/P4 doses only[6]
  - Study treatments were taken orally at bedtime with food
- Eligible women were between the ages of 40 and 65 years, postmenopausal, and seeking treatment or relief for VMS associated with menopause[6]
- All women in the REPLENISH study completed a daily bleeding/spotting diary
  - Spotting: women did not require sanitary protection
  - Bleeding: required sanitary protection
  - Amenorrhea: no bleeding or spotting
- The number of days with bleeding and/or spotting was summarized by cycle and treatment

Vaginal Bleeding Predictors

- Univariate analyses were used to assess the impact of baseline characteristics including age, race, body mass index (BMI), smoking, time since last menstrual period (LMP), age at LMP, tubal ligation, parity, E2 concentration, and frequency and severity of VMS (mild=1 to severe=3) on the incidence of vaginal bleeding at any time during the study (cumulative incidence at cycle 13) and bleeding that occurred in the first 3 months of the study (cumulative incidence at cycle 3)
- Correlation analysis and logistic regression were used to calculate the odds ratio (OR) of bleeding/spotting ≥4 days/week vs <4 days/week with respect to serum E2 and estrone (E1) concentrations

Results

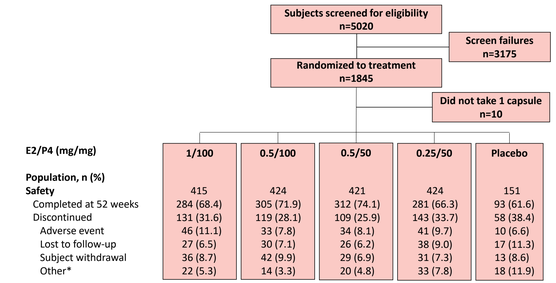
Patient Disposition and Demographics

- A total of 1845 women were randomized and 1835 took at least one capsule of study drug (safety population; **Figure 2**); 1275 (69.5%) women completed 52 weeks
- The overall discontinuation rate from the study at 12 months was lower with E2/P4 (28.3%) than with placebo (38.4%)
- Mean age was 55 years and mean BMI was 27 kg/m^2; 65% of participants were white and 32% were African American

Vaginal Bleeding Predictors

- Significant predictors of vaginal bleeding with E2/P4 (at cycle 13) included age, time since LMP, E2 concentration, and severity of VMS (**Table 1**). The likelihood of bleeding was:
  - Reduced by 42% for every 5-year increase in age (*P*<0.0001)
  - Reduced by 39% for every 5-year increase in time since LMP (*P*<0.0001)
  - Reduced by 54% with baseline E2 levels <10 pg/mL (*P*=0.0001), 59% with E2 levels <5 pg/mL (*P*<0.0001), and 48% for E2 levels 5 to <10 pg/mL (*P*=0.004), when compared with E2 levels ≥10 pg/mL
  - Reduced by 33% in women with less severe VMS (<2.5 points)

Figure 2. Disposition of study participants



E2/P4 (mg/mg)	1/100	0.5/100	0.5/50	0.25/50	Placebo
Population, n (%)					
Safety	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	131 (31.6)	119 (28.1)	109 (25.9)	143 (33.7)	58 (38.4)
Adverse event	46 (11.1)	33 (7.8)	34 (8.1)	41 (9.7)	10 (6.6)
Lost to follow-up	27 (6.5)	30 (7.1)	26 (6.2)	38 (9.0)	17 (11.3)
Subject withdrawal	36 (8.7)	42 (9.9)	29 (6.9)	31 (7.3)	13 (8.6)
Other*	22 (5.3)	14 (3.3)	20 (4.8)	33 (7.8)	18 (11.9)

- Similar predictors were noted for bleeding at cycle 3, except for baseline VMS severity, which was not a significant predictor
- No statistically significant differences in reports of bleeding were noted for race, BMI, smoking, age at LMP, tubal ligation, parity, or baseline frequency of moderate to severe VMS (**Table 1**)

Table 1. Predictors of bleeding with baseline characteristics at cycle 13 or cycle 3

Parameters		Cycle 13 OR (95%CI)	Cycle 3 OR (95% CI)
Age, y	5-year increase	**0.58 (0.48–0.70)**	**0.59 (0.47–0.73)**
Race	White vs black	0.88 (0.64–1.21)	0.91 (0.63–1.31)
BMI, kg/m^2	25 to <30 vs <25	1.19 (0.83–1.73)	0.99 (0.65–1.51)
	30+ vs <25	1.34 (0.90–1.98)	1.21 (0.78–1.89)
Smoking	Current vs never	1.34 (0.92–1.95)	1.42 (0.93–2.189)
	Former vs never	1.17 (0.82–1.68)	1.24 (0.82–1.87)
Time since LMP	5-year increase	**0.61 (0.50–0.75)**	**0.65 (0.52–0.82)**
Age at LMP	5-year increase	0.97 (0.82–1.16)	0.92 (0.76–1.12)
Tubal ligation	Yes vs no	1.11 (0.80–1.52)	0.98 (0.68–1.40)
Parity	Yes vs no	0.72 (0.45–1.13)	0.71 (0.42–1.20)
Baseline E2 levels, pg/mL	5 to <10 vs ≥10	**0.53 (0.35–0.82)**	**0.57 (0.36–0.92)**
	<5 vs ≥10	**0.42 (0.27–0.63)**	**0.36 (0.22–0.57)**
	<10 vs ≥10	**0.46 (0.31–0.69)**	**0.45 (0.29–0.69)**
Frequency of moderate to severe VMS	50+/wk vs <50/wk	0.94 (0.69–1.27)	1.03 (0.72–1.46)
	70+/wk vs <70/wk	1.43 (0.98–2.09)	1.10 (0.70–1.73)
Severity of VMS	1-point increase	1.27 (0.90–1.80)	1.15 (0.77–1.71)
	<2.5-point vs ≥2.5-point	**0.67 (0.46–0.96)**	0.67 (0.45–1.02)

- Weak, but significant, correlations with baseline E2 and E1 levels were observed with the weekly number of days of bleeding/spotting at week 12 (E2: *r*=0.07, *P*<0.009; E1: *r*=0.088, *P*<0.0004)
  - Women with higher baseline E1 levels, but not E2 levels, were 4.8 times more likely to have ≥4 versus <4 days of bleeding/spotting at week 12 (**Table 2**)
- Serum on-therapy concentrations of E2 and E1 at week 12 were also significantly weakly correlated with the weekly number of bleeding/spotting days at week 12 (E2: *r*=0.148, *P*<0.0001 and E1: *r*=0.116, *P*<0.0001)
  - Women with higher E2 levels were 9.3 times more likely and those with higher E1 levels were 7.0 times more likely to have ≥4 versus <4 days of bleeding/spotting at week 12 (**Table 2**)

Table 2. Odds ratio of weekly number of bleeding/spotting days (4+ vs <4 days) with E1 and E2 levels

Parameters	Levels	Week 12 OR (95% CI)
E2 levels		
Baseline	high vs low	2.51 (0.89–7.10)
Week 12	high vs low	**9.34 (4.02–21.7)**
E1 levels		
Baseline	high vs low	**4.76 (1.05–21.6)**
Week 12	high vs low	**6.96 (2.69–18.0)**

CI, confidence interval; E1, estrone; E2, estradiol; OR, odds ratio.

Conclusions

- Cumulative amenorrhea was high in E2/P4 users of the REPLENISH trial[6]
- Older women, those with a less recent LMP, and women with lower baseline E2 concentrations were less likely to experience vaginal bleeding while using E2/P4
- Even though the rate/amount of bleeding was relatively low overall,[6] these data may help clinicians inform women who may be more likely to experience vaginal bleeding while taking combined, bioidentical E2/P4 for menopausal symptoms

References

1. Prempro™/Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets) Prescribing Information. *Wyeth Pharmaceuticals Inc.* Philadelphia, PA. 2008. **2.** Activella® (estradiol/norethindrone acetate) tablets. *Novo Nordisk Inc.* Princeton, NJ. 2006. **3.** Angeliq® (drospirenone and estradiol) tablets, for oral use Prescribing Information. *Bayer Healthcare.* Whippany, NJ. 2005. **4.** Climara® (estradiol transdermal system) Prescribing Information. *3M Drug Delivery Systems.* Northridge, CA. 2007. **5.** CombiPatch® (estradiol/norethindrone acetate transdermal system) Prescribing Information. *Novartis Pharmaceuticals Corporation.* East Hanover, NJ. 2005. **6.** Lobo RA, et al. *Obstet Gynecol.* 2018;132:161-170.

Disclosures

- GC consults to multiple pharmaceutical companies including but not limited to TherapeuticsMD and has stock options from TherapeuticsMD. SRG is on the advisory board of AbbVie, Allergan, IBSA, Pfizer, and TherapeuticsMD; and consults for Cook ObGyn and Cooper Surgical. JHP consults for Pfizer, Shionogi, and TherapeuticsMD; and has stock options with TherapeuticsMD. SG, BB, and SM are employees of TherapeuticsMD with stock/stock options. BB is also a Board member of TherapeuticsMD.
- TherapeuticsMD sponsored the study and supported the medical writing assistance provided by Dominique Verlaan, PhD (Precise Publications, LLC).

ENDO 2019 Meeting, March 23-26, New Orleans, LA