Bioidentical Estradiol and Progesterone Improved Hot Flushes, Night Sweats and Sweating

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Introduction

- Vasomotor symptoms (VMS), including hot flushes, night sweats, and sweating are a common complaint of postmenopausal women[1,2]
  - Moderate to severe VMS can be effectively treated with FDA-approved hormone therapy (HT)[3]
- The phase 3 REPLENISH trial evaluated four daily oral doses of E2/P4 combination capsules in postmenopausal women with a uterus; the primary efficacy and safety endpoints have been published by Lobo et al[4]
  - Briefly, the two highest doses of E2/P4 reduced the frequency and severity of moderate to severe hot flashes (**Figure 1**)[4] and improved quality of life outcomes as assessed by the menopause-specific quality of life (MENQOL) questionnaire (**Figure 2**),[5] while protecting the endometrium[4]
- In October 2018, the US Food and Drug Administration (FDA) approved the 1 mg E2/100 mg P4 dose as Bijuva™ (TherapeuticsMD, Boca Raton, FL), the first bioidentical oral HT, for the treatment of moderate to severe VMS due to menopause in women with a uterus

Figure 1. Weekly improvement in frequency and severity of moderate to severe VMS[4]

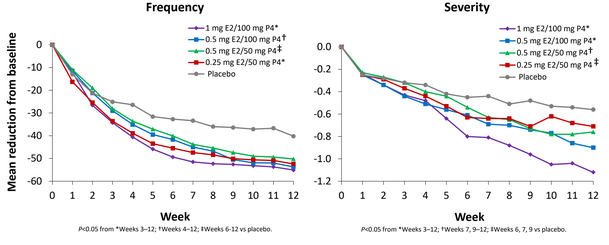
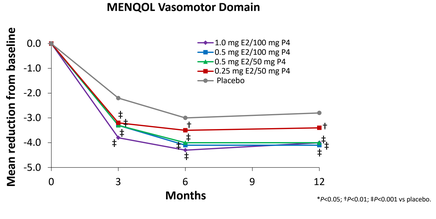


Figure 2. Change from baseline in the MENQOL vasomotor domain[5]



Objective

To evaluate the effect of E2/P4 on hot flushes, night sweats and sweating in postmenopausal women experiencing VMS as assessed by MENQOL

Methods

Study Design

- The REPLENISH trial (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial of E2/P4 capsules in postmenopausal women, which included a 1-year endometrial safety study and 12-week efficacy substudy for treatment of VMS[4]
- Participants had to be 40 to 65 years of age and postmenopausal, have a uterus and BMI ≤34 kg/m^2, and be seeking treatment or relief for VMS associated with menopause[4]
- Women with moderate to severe hot flushes (≥7/day or ≥50/week) were randomized to daily oral E2/P4 (mg/mg) 1/100, 0.5/100, 0.5/50, 0.25/50 or placebo in a VMS substudy; other women (with less frequent VMS) were randomized to E2/P4 doses only for endometrial assessment in the general study[4]
- Participants in the modified intent-to-treat (MITT) population had taken ≥1 treatment dose; those in the MITT-VMS population (primary efficacy population) had been randomized to the VMS substudy and had taken ≥1 treatment dose with the requisite on-treatment diary data reporting VMS frequency and severity

MENQOL Hot Flushes, Night Sweats, and Sweating

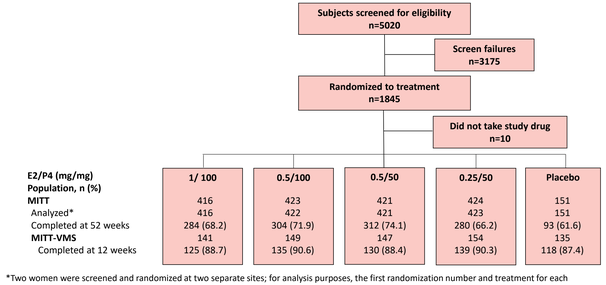
- One secondary endpoint of the trial was to assess quality of life outcomes using the MENQOL questionnaire (29 questions), which was self-administered at baseline, week 12, and months 6 and 12
- Individual items of the MENQOL vasomotor domain (hot flushes [question #1], night sweats [#2], and sweating [#3]) were assessed
  - Items were rated using a 7-item Likert scale ranging from "Not at all bothered" (score of 2) to "Extremely bothered" (score of 8); if not experienced, the score was set to 1
- Changes from baseline to week 12, and months 6 and 12 in the MITT and MITT-VMS populations were analyzed post hoc by ANCOVA between each E2/P4 dose vs placebo

Results

Study Disposition and Demographics

- A total of 1845 women were randomized and 1833 were in the MITT population; 1273 (69%) completed 52 weeks (**Figure 3**)
- Of the 726 in the MITT-VMS population, 647 (89%) completed the 12-week efficacy VMS substudy
- Women in the VMS substudy had a mean age of 55 years (range, 40-65 years) and mean BMI of 27 kg/m^2; 67% were white and 31% were African American; similar demographics were observed in the MITT population

Figure 3. Patient disposition



E2/P4 (mg/mg)	1/ 100	0.5/100	0.5/50	0.25/50	Placebo
Population, n (%)					
MITT	416	423	421	424	151
Analyzed*	416	422	421	423	151
Completed at 52 weeks	284 (68.2)	304 (71.9)	312 (74.1)	280 (66.2)	93 (61.6)
MITT-VMS	141	149	147	154	135
Completed at 12 weeks	125 (88.7)	135 (90.6)	130 (88.4)	139 (90.3)	118 (87.4)

*Two women were screened and randomized at two separate sites; for analysis purposes, the first randomization number and treatment for each woman was utilized

MENQOL Vasomotor Domain: Hot Flushes, Night Sweats, and Sweating

MITT Population

- Mean baseline scores ranged from 6.7-7.4 points for hot flushes, 6.1-7.1 points for sweating, and 6.0-6.9 points for night sweats
- Women treated with all E2/P4 doses had significantly more favorable improvements from baseline in hot flushes, night sweats, and sweating than with placebo (**Figure 4**)
  - Significant mean changes with E2/P4 vs placebo ranged from -1.3 to -2.2 for hot flushes, -1.0 to -1.9 for night sweats, and -0.7 to -1.7 for sweating (all, *P*<0.001)

MITT-VMS Population

- Mean baseline scores ranged from 7.3-7.4 points for hot flushes, 6.9-7.1 points for sweating, and 6.7-6.9 points for night sweats
- Hot flushes, night sweats, and sweating improved more favorably at all timepoints with E2/P4 versus placebo in the MITT-VMS population, similar to the MITT population (except with 0.25 mg E2/50 mg P4 at months 6 and 12 for sweating) (**Figure 5**)
  - Significant mean changes with E2/P4 vs placebo ranged from -0.9 to -1.8 for hot flushes (all, *P*<0.001), -0.7 to -1.7 for night sweats (all, *P*<0.05), and -0.8 to -1.5 for sweating (all, *P*<0.01)

Figure 4. Changes from baseline and changes from placebo in the MENQOL (A) hot flushes, (B) night sweats, and (C) sweating in MITT population

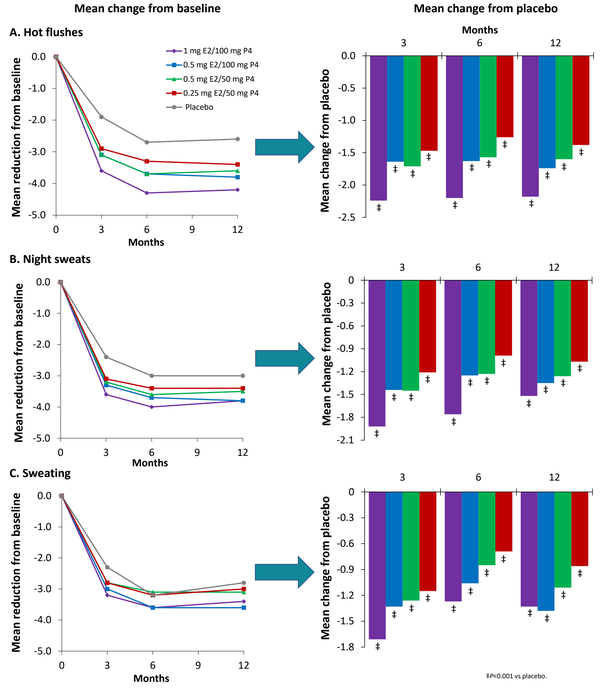
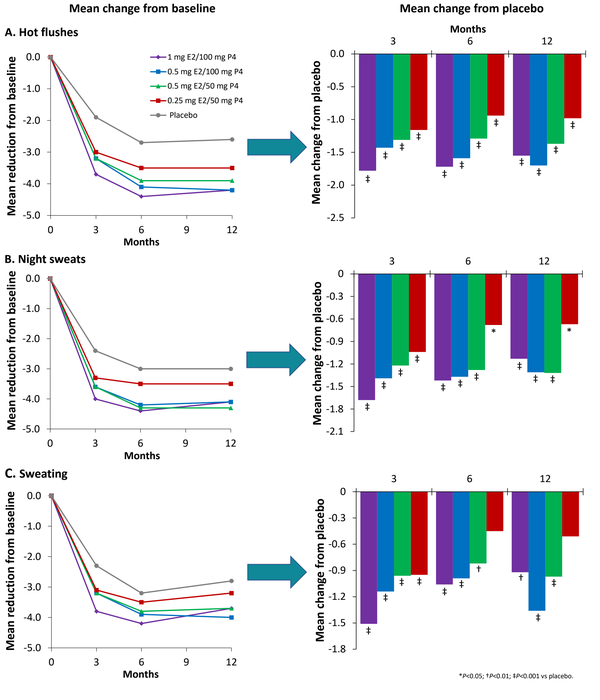


Figure 5. Changes from baseline and changes from placebo in the MENQOL (A) hot flushes, (B) night sweats, and (C) sweating in MITT-VMS population



Conclusions

- In REPLENISH, postmenopausal women treated with E2/P4 had significant and sustained improvements compared with placebo in hot flushes, night sweats, and sweating as assessed by MENQOL
  - Improvements in symptoms continued for up to 12 months with E2/P4
- These results are consistent with the primary results of the REPLENISH trial demonstrating efficacy for the treatment of moderate to severe VMS[4] and improved quality of life outcomes[5]
- The 1 mg E2/100 mg P4 dose, the first combined bioidentical oral E2/P4 product that is FDA-approved, Bijuva, represents a new oral HT option for postmenopausal women with moderate to severe VMS and a uterus

References

1. Hunter MS, et al. *BJOG*. 2012;119:40-50. **2.** Duffy OK, et al. *BJOG*. 2012;119:554-564. **3.** The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. *Menopause*. 2017;24:728-753. **4.** Lobo RA, et al. *Obstet Gynecol*. 2018;132:161-170. **5.** Simon JA, et al. *Menopause*. 2018 [Epub ahead of print, Nov 26].

Disclosures

- JHL consults for Allergan, Bayer Healthcare, Pfizer, and TherapeuticsMD and has received research support (paid to UH Cleveland Medical Center) from AbbVie, Allergan, Bayer Healthcare, Ferring, and Palatin. AMK consults for or is on the advisory board of AMAG, Mithra, Pfizer, and Shionogi and has received research support (paid to the University of FL) from Bayer Healthcare, Endoceutics, and TherapeuticsMD. JAS has served (within the past year, or current) as a consultant/advisor to AbbVie, Allergan plc, AMAG, Amgen, Ascend Therapeutics, Bayer Healthcare, CEEK Enterprises, Covance, Dare Bioscience, Duchesnay, Hologic, KaNDy/NeRRe Therapeutics, Mitsubishi Tanage, ObsEva SA, Palatin Technologies, Sanofi SA, Shionogi, Sprout, and TherapeuticsMD; has received (within the past year, or current) grant/research support from AbbVie, Agile Therapeutics, Allergan plc, Bayer Healthcare, Endoceutics, GTx, Ipsen, Myovant Sciences, New England Research Institute, ObsEva SA, Palatin Technologies, Symbio Research, TherapeuticsMD, and Vivwe Medical; has also served (within the past year, or current) on the Speakers' Bureaus of AbbVie, AMAG, Duchesnay, Novo Nordisk, Shionogi, and TherapeuticsMD and is a stockholder (direct purchase) in Sermonix Pharmaceuticals. BB and SM are employees of TherapeuticsMD with stock/stock options. BB is also a Board member of TherapeuticsMD.
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