Combined Bioidentical Estradiol and Progesterone Capsules Improved Quality of Sleep in Postmenopausal Women with Vasomotor Symptoms

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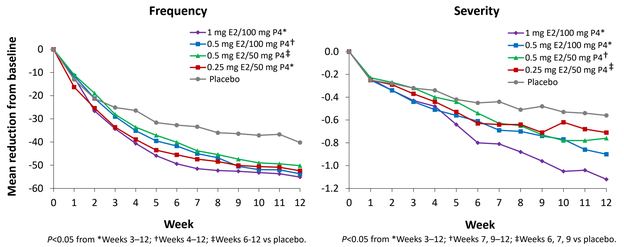
Introduction

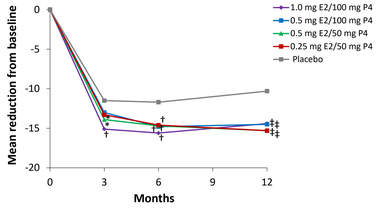
- Vasomotor symptoms (VMS) in menopausal women can be bothersome[1-3] and negatively impact quality of life,[1,4] sleep,[1,5] and work productivity[4,6]
  - Difficulty sleeping is a common complaint of postmenopausal women,[2,3] and has been associated with VMS[7-10]
- Moderate to severe VMS can be effectively treated with approved hormone therapy (HT)
- The phase 3 REPLENISH trial in postmenopausal women with a uterus showed that the two highest daily doses of combined E2/P4 oral HT capsule reduced frequency and severity of VMS (**Figure 1**)[11] and improved quality of life outcomes,[12] including sleep (**Figure 2**),[13] while protecting the endometrium[11]
  - In October 2018, the US Food and Drug Administration (FDA) approved combined bioidentical 1 mg E2/100 mg P4 capsules as Bijuva™ (TherapeuticsMD, Boca Raton, FL) for treating menopausal, moderate to severe VMS in women with a uterus

Figure 1. Weekly improvement in frequency and severity of moderate to severe hot flushes



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.

Figure 2. Improvement in the Medical Outcome Study (MOS)-Sleep total score



P<0.05; †*P*<0.01; ‡*P*<0.001 vs placebo.

Objective

To evaluate the effect of E2/P4 on "difficulty sleeping" in postmenopausal women experiencing hot flushes, as assessed by the Menopause-specific Quality of Life (MENQOL) questionnaire, including an analysis by age

Methods

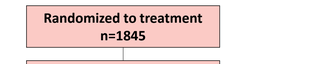
Study Design

- The REPLENISH trial (NCT01942668) was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of E2/P4 capsules in postmenopausal women[11]
- Healthy menopausal women (aged 40-65 years; BMI ≤34 kg/m^2) with a uterus were eligible. Key inclusion and exclusion criteria have been previously reported[11]
- 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 with less frequent VMS were randomized to E2/P4 doses only for endometrial assessment in the general study[11]
- Primary endpoints were to evaluate the efficacy and safety of 4 daily doses of E2/P4 combination capsules versus placebo for treatment of moderate to severe VMS (**Figure 1**)[11]
- One secondary endpoint 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
- The modified intent-to-treat (MITT) population included participants who took ≥1 dose of treatment

MENQOL "difficulty sleeping"

- The MENQOL difficulty sleeping item (question #14) was rated using a 7-item Likert scale ranging from "Not at all bothered" (score of 2) to "Extremely bothered" (score of 8) if difficulty sleeping was experienced; if not experienced, the score was set to 1
- Changes from baseline to week 12, and months 6 and 12 in all women (MITT population) were analyzed post hoc by ANCOVA between each E2/P4 group vs placebo and were also stratified by age (pre-specified FDA subgroup; <55 and 55+)

Figure 3. Patient disposition



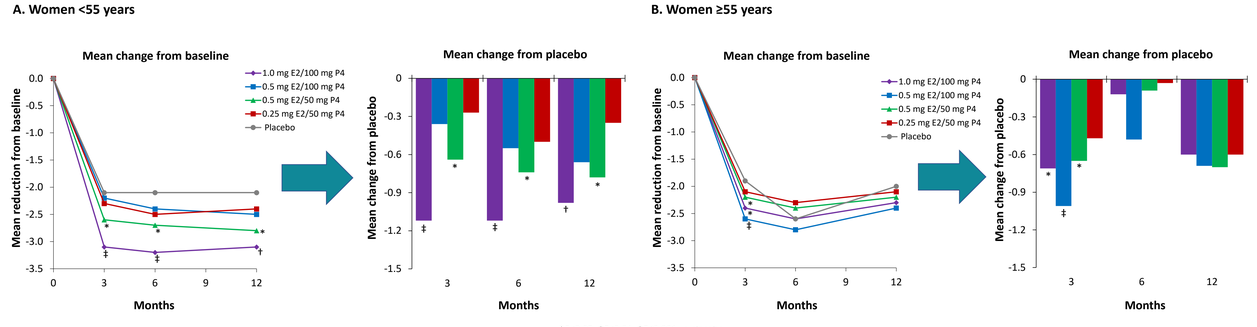
E2/P4 (mg)	1/100	0.5/100	0.5/50	0.25/50	Placebo
Population, n (%)					
MITT	416	422	421	423	151
<55 years	200 (48.1)	226 (53.6)	197 (46.8)	227 (53.7)	77 (51.0)
≥55 years	216 (51.9)	196 (46.4)	224 (53.2)	196 (46.3)	74 (49.0)
Completed at 52 weeks	284 (68.2)	304 (71.9)	312 (74.1)	280 (66.2)	93 (61.2)

Results

Study Disposition and Demographics

- A total of 1833 women were included (MITT population; **Figure 3**); 69% of women completed 52 weeks
- Mean age was 51.2 years for women <55 years (n=927) and 58.1 years for women ≥55 years (n=906); mean BMI was 27 kg/m^2 for both age groups

Figure 5. Mean changes from baseline and placebo in the MENQOL difficulty sleeping score for women (A) <55 years or (B) ≥55 years

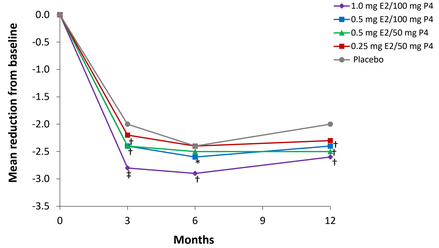


P<0.05; †*P*<0.01; ‡*P*≤0.001 vs placebo.

MENQOL "difficulty sleeping"

- Mean baseline scores for "difficulty sleeping" ranged from 5.1 to 5.8 points, with similar ranges for women <55 years (5.3–5.8 points) and ≥55 years (5.1–5.8 points)
- In the MITT population, the difficulty sleeping score significantly improved from baseline with the three highest E2/P4 doses compared with placebo at all timepoints (all, *P*<0.05), except for 0.5/50 at month 6 (**Figure 4**)
  - In women <55 years, significant improvements from baseline were observed with two E2/P4 doses (1/100 and 0.5/50) vs placebo at all timepoints (**Figure 5A**)
  - In women ≥55 years, significant improvements from baseline were observed with three E2/P4 doses (1/100, 0.5/100, 0.5/50) vs placebo at week 12 only (**Figure 5B**)

Figure 4. Change from baseline in the MENQOL difficulty sleeping score (MITT population)



P<0.05; †*P*<0.01; ‡*P*<0.001 vs placebo.

Conclusions

- E2/P4 (1/100 and 0.5/50) improved sleep as measured by MENQOL. These data support previous reports of sleep improvement due to decreases in the frequency and severity of moderate to severe hot flushes as measured by MOS-Sleep scale in the REPLENISH trial[13,14]
- Overall, women <55 years had more significant and sustained improvements in the MENQOL difficulty sleeping assessment with E2/P4 (1/100 and 0.5/50) vs placebo compared with women ≥55 years, which may be partly due to a large placebo response in women ≥55 years
- As the first combined bioidentical E2/P4 oral product approved by the FDA, 1 mg E2/100 mg P4 (Bijuva), is a new oral HT option for postmenopausal women with moderate to severe VMS and a uterus, including the estimated millions[15,16] of US women using unapproved compounded bioidentical hormones

References

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Disclosures

- NS is on the advisory board of Astellas/Ogeda and Menogenix. GC consults for multiple pharmaceutical companies including but not limited to TherapeuticsMD and has stock options with TherapeuticsMD. RK consults for Allergan, Cooper Surgical, Duchesnay, Lupin, Noven, Proctor & Gamble, Radius Health, and TherapeuticsMD and is on the speaker's bureau of AMAG, Cooper Surgical, and 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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