Effects of TX-001HR in Women with <50 Moderate to Severe Hot Flushes per Week

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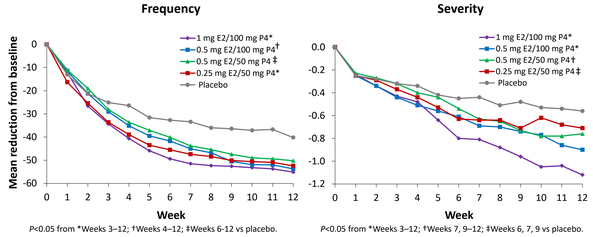
Introduction

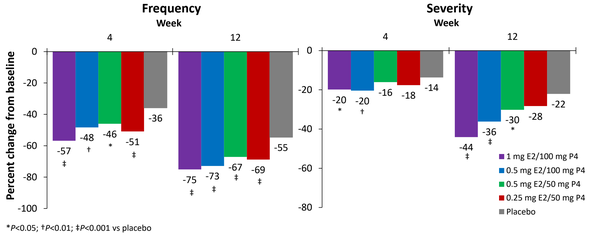
- Vasomotor symptoms (VMS) are a common complaint of postmenopausal women[1,2]
  - Moderate to severe VMS can be effectively treated with FDA-approved hormone therapy (HT)[3]
  - While most women do not meet the FDA criteria for ≥50 moderate to severe VMS per week, they are still bothered by their VMS
- In the phase 3 REPLENISH trial evaluating four daily oral doses of 17β-estradiol/progesterone (E2/P4) capsules in postmenopausal women,[4] E2/P4
  - Reduced the frequency and severity of moderate to severe VMS in women with ≥50 moderate to severe VMS per week (two highest doses; efficacy population; **Figures 1 and 2**)[4]
  - Improved quality of life outcomes[5,6]
  - Protected the endometrium[4]
- In October 2018, the FDA approved the 1 mg E2/100 mg P4 capsules as Bijuva™ (TherapeuticsMD, Boca Raton, FL) for treating moderate to severe VMS in postmenopausal women with a uterus

Figure 1. Weekly improvement in frequency and severity of moderate to severe VMS in women with ≥50 moderate to severe VMS/week[4]



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. Mean percent improvement in frequency and severity at weeks 4 and 12 in women with ≥50 moderate to severe VMS/week[4]



*P<0.05; †P<0.01; ‡P<0.001 vs placebo

Objective

To evaluate the effects of E2/P4 on VMS frequency and severity in women with <50 moderate to severe VMS/week

Methods

Study Design

- The REPLENISH trial (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that evaluated the safety and efficacy of four E2/P4 doses in postmenopausal women[4]
- Eligible women had a uterus and were between the ages of 40 and 65 years, postmenopausal, and seeking relief for VMS[4]
- Women with moderate to severe VMS (≥7/day or ≥50/week) were included in a VMS substudy and were randomized to daily oral E2/P4 (mg/mg) of 1/100, 0.5/100, 0.5/50, or 0.25/50, or placebo for 12 months; women with less frequent VMS were randomized to E2/P4 doses only for endometrial and safety assessments[4]
- For this post hoc analysis, participants with **<50 moderate to severe VMS per week** who had taken ≥1 on-treatment dose with diary data reporting VMS frequency and severity **(VMS-non–substudy)** were included

VMS Frequency and Severity

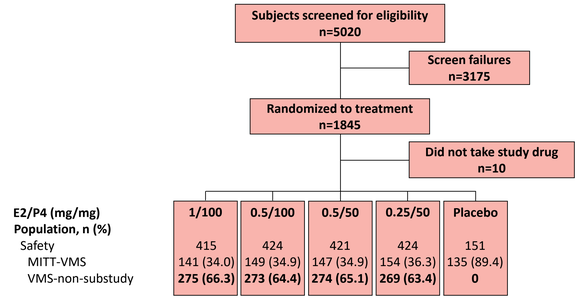
- All women completed a daily diary on the frequency and severity of their VMS through week 12
  - Weekly frequency = total number of VMS per week
  - Weekly severity = [(number of mild VMS per week x 1) + (number of moderate VMS per week x 2) + (number of severe VMS per week x 3)]/(total weekly number of mild, moderate and severe VMS)
- Mean changes and percent changes from baseline in frequency and severity of VMS at weeks 4 and 12 was evaluated in the VMS-non–substudy population

Results

Study Disposition and Demographics

- 1091 women with <50 moderate to severe VMS/week were randomized to the active E2/P4 doses and included in this analysis (**Figure 3**)

Figure 3. Patient disposition



E2/P4 (mg/mg) Population, n (%)	1/100	0.5/100	0.5/50	0.25/50	Placebo
Safety	415	424	421	424	151
MITT-VMS	141 (34.0)	149 (34.9)	147 (34.9)	154 (36.3)	135 (89.4)
VMS-non-substudy	**275 (66.3)**	**273 (64.4)**	**274 (65.1)**	**269 (63.4)**	**0**

Figure 4. Mean change from baseline in VMS frequency and severity

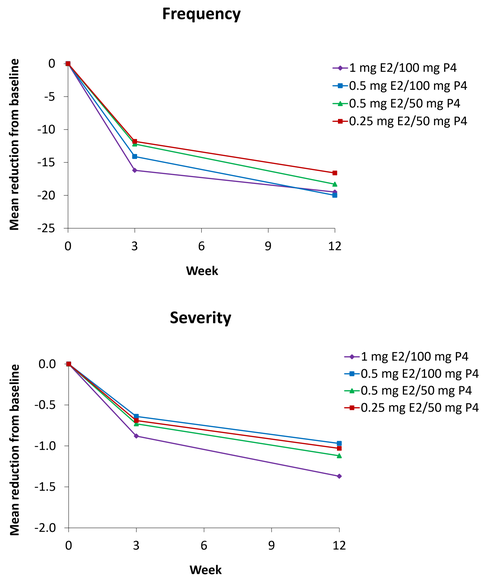
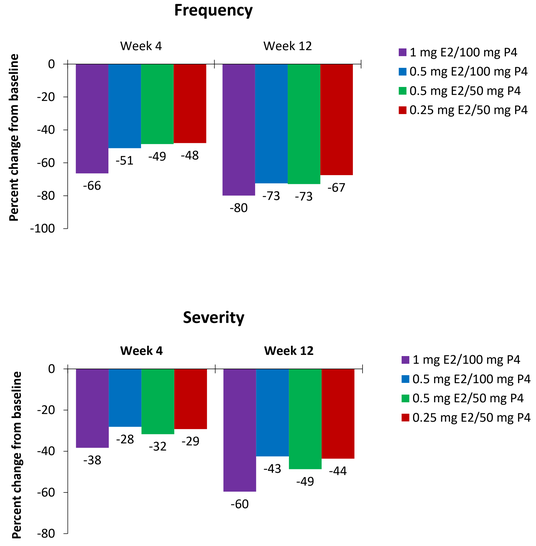


Figure 5. Mean percent change from baseline in VMS frequency and severity



VMS Frequency and Severity

- Baseline mean number of VMS in the VMS-non–substudy was 24.4-27.6 per week and mean severity score was 2.28-2.36
- Women treated with E2/P4 doses had improvements from baseline in (**Figure 4**)
  - Frequency of 11.8-16.2 VMS at week 4 and 16.6-19.5 VMS at week 12
  - Severity of 0.64-0.88 points at week 4 and 0.97-1.37 points at week 12
- Women treated with E2/P4 doses had mean percent improvements from baseline in (**Figure 5**)
  - Frequency of 48%-66% at week 4 and 67%-80% at week 12
  - Severity of 28%-38% at week 4 and 43%-60% at week 12

Conclusions

- The magnitude of improvements in frequency and severity observed with E2/P4 in women with <50 moderate to severe VMS/week was similar to the significant improvements previously reported (Lobo et al, 2018)[4] in women with ≥50 moderate to severe VMS/week for frequency (67%-75%) and severity (30%-44%) at week 12
- A limitation of this analysis was that there was no placebo group in the VMS-non–substudy
- The benefits of an oral E2/P4 capsule may extend to women who have less frequent moderate to severe VMS than what is typically studied and required for regulatory approval, but similar to what most women in the general population experience while going through menopause

Disclosures

- RK consults to Allergan, Cooper Surgical, Duchesnay, Lupin, Noven, Procter & Gamble, Radius Health, and TherapeuticsMD; and serves on the speaker's bureau for AMAG, Cooper Surgical, and TherapeuticsMD. GC consults for multiple pharmaceutical companies including but not limited to TherapeuticsMD and has stock options from 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 of Dominique Verlaan, PhD (Precise Publications, LLC).

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]. **6.** Kagan R, et al. *Menopause*. 2018 [Epub ahead of print, Dec 21].

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