Bioidentical Combined Estradiol and Progesterone Capsules Improved Vaginal Dryness in Women with Vasomotor Symptoms

James A Simon, MD[1]; Sharon J Parish, MD[2]; Brian Bernick, MD[3]; Shelli Graham, PhD[3]; Sebastian Mirkin, MD[3]

[1]George Washington University School of Medicine, IntimMedicine Specialists, Washington, DC; [2]Weill Cornell Medical College, New York, NY; [3]TherapeuticsMD, Boca Raton, FL

Disclosures

- **Consultant/Advisory board:** 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
- **Research grants:** AbbVie, Agile Therapeutics, Allergan plc, Bayer Healthcare, Endocuetics, GTx, Ipsen, Myovant Sciences, New England Research Institute, ObsEva SA, Palatin Technologies, Symbio Research, TherapeuticsMD, and Viveve Medical
- **Speaker's bureau:** AbbVie, AMAG, Duchesnay, Novo Nordisk, Shionogi, and TherapeuticsMD
- **Stockholder:** Sermonix Pharmaceuticals

Background

- Many postmenopausal women experience bothersome symptoms during menopause, including vasomotor symptoms (VMS) and vulvovaginal atrophy[1-3]
  - Symptoms can be effectively treated with HT[4]
- Use of compounded bioidentical HT (estradiol [E2] and progesterone [P4]) has become highly prevalent in the US since the 2002 WHI report[5]
  - An estimated 1 to 2.5 million US women use unapproved compounded products,[5,6] representing up to 21 to 39 million prescriptions annually[5]
  - Some compounded products may be associated with increased risks[7]
  - An FDA-approved E2/P4 combination may be a possible alternative for postmenopausal women with VMS who prefer bioidentical hormones
- 1 mg E2/100 mg P4 was approved by the FDA as Bijuva™ (October 2018) for the treatment of moderate to severe VMS in postmenopausal women with a uterus

HT: hormone therapy; WHI: Women's Health Initiative.

1. Blumel JE, et al. *Menopause.* 2011;18:778-785. **2.** Hunter MS, et al. *BJOG.* 2012;119:40-50. **3.** Duffy OK, et al. *BJOG.* 2012;119:554-564. **4.** ACOG. *Obstet Gynecol.* 2014;123:202-216. **5.** Pinkerton J and Santoro N. *Menopause* 2015;22:926-936. **6.** Pinkerton J and Constantine G. *Menopause* 2016;23:359-367. **7.** Pinkerton J and Pickar JH. *Menopause.*2015;23:215-223.

REPLENISH Trial: Objective and Design

Primary objectives: To evaluate the efficacy and safety of four doses of an oral softgel capsule combining bioidentical E2/P4 (TX-001HR) versus placebo for the treatment of moderate to severe vasomotor symptoms (VMS)

Design: Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of TX-001HR in menopausal women with an intact uterus (NCT01942668)

- 1-year endometrial safety study and 12-week efficacy substudy for the treatment of VMS

Secondary endpoint: Menopause-specific Quality of Life (MENQOL) questionnaire, which consists of 30 questions on quality of life

- **Post hoc analysis:** MENQOL item "vaginal dryness during intercourse" in women younger or older than 55 years

Lobo RA, et al. *Obstet Gynecol* 2018;132:161-170.

Key Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Healthy menopausal women aged 40-65 years • Intact uterus • BMI ≤34 kg/m^2 • VMS associated with menopause • Acceptable endometrial biopsy results <u>VMS Substudy</u> • ≥7/day or ≥50/week moderate-to-severe hot flushes	• History of hyperplasia or neoplasia of hormone dependent tissues • History of thrombosis of deep veins/arteries • Abnormalities of the gastrointestinal system • Abnormal function of other hormone producing glands • Recent use (1 to 12 weeks) of estrogen-, progestogen-, androgen-, SERM products • Medications known to induce or affect estrogen and/or progestogen drug metabolism or activity

BMI: body mass index; SERM: selective estrogen receptor modulator; VMS: vasomotor symptoms.

Lobo RA, et al. *Obstet Gynecol* 2018;132:161-170.

Study Design: Randomization

VMS substudy (12 wks)

- ≥7/day or ≥50/week moderate-to-severe hot flushes
- Randomized 1:1:1:1:1

Treatment Groups

- 1 mg E2/100 mg P4
- 0.5 mg E2/100 mg P4
- 0.5 mg E2/50 mg P4
- 0.25 mg E2/50 mg P4
- Placebo

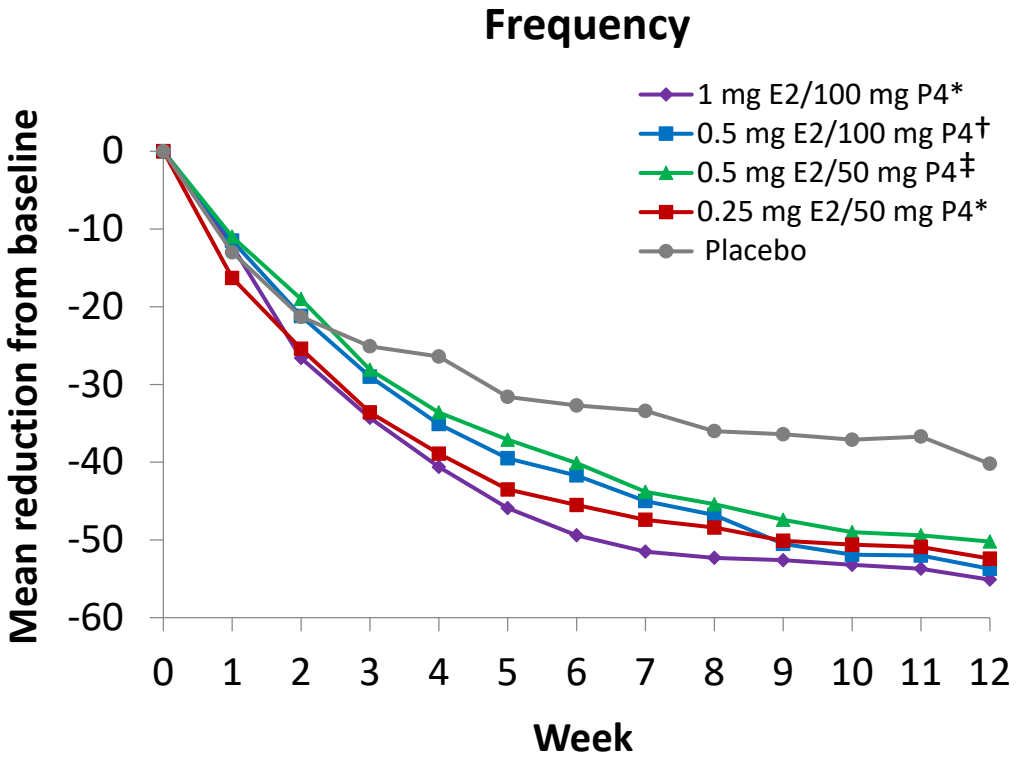
General study (12 mos)

- Did not qualify for VMS substudy
- Randomized 1:1:1:1

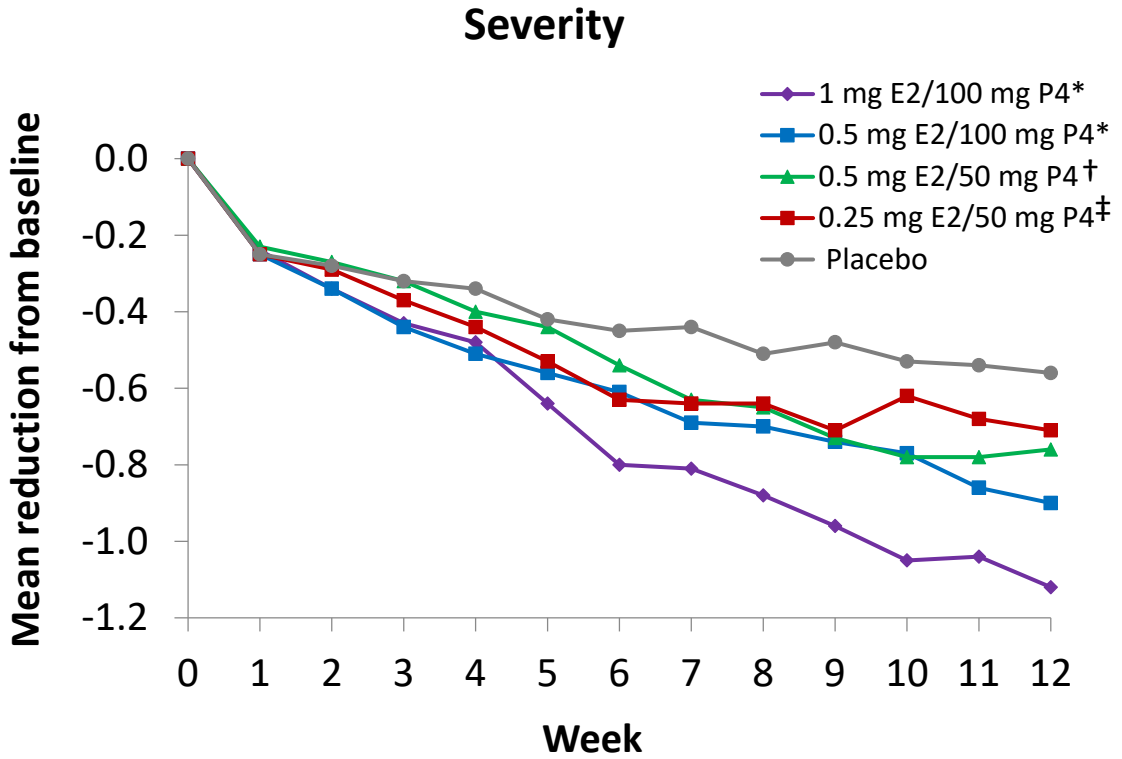
- TX-001HR was taken daily for 12 months (VMS substudy was 12 weeks)

VMS Frequency and Severity

- E2/P4 oral capsules reduced the frequency and severity of moderate to severe hot flushes (Figures)[1] and improved quality of life outcomes[2]



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.

1. Lobo RA, et al. *Obstet Gynecol* 2018;132:161-170. **2.** Simon JA, et al. *Menopause.* 2018 [Epub ahead of print, Nov 26].

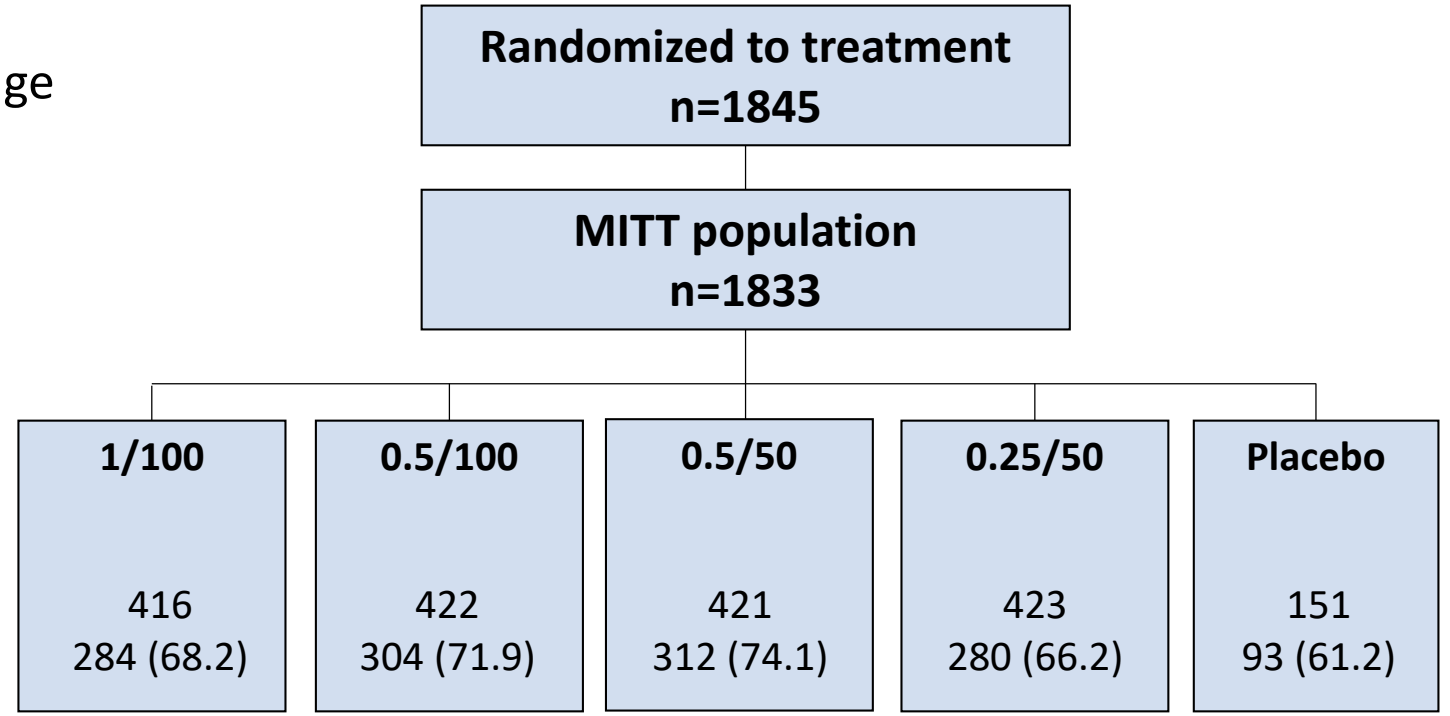
Post Hoc Analysis

- To determine the effects of the E2/P4 capsules versus placebo on vaginal dryness in postmenopausal women (younger or older than 55 years) experiencing VMS using the MENQOL questionnaire (secondary endpoint)
- MENQOL item "**Vaginal dryness during intercourse**" was evaluated at baseline, week 12, and months 6 and 12
  - If not experienced, the analysis score was set to 1
  - If experienced, it was rated using a 7-item Likert scale ranging from "Not at all bothered" (score of 2) to "Extremely bothered" (score of 8)

MENQOL: Menopause-Specific Quality of Life.

Disposition and Demographics

- 69% of women completed at 52 weeks
- Mean age for women
  - <55 years (n=927) = 51.2 years
  - ≥55 years (n=906) = 58.1 years
- Mean BMI was the same for both age groups: 27 kg/m^2

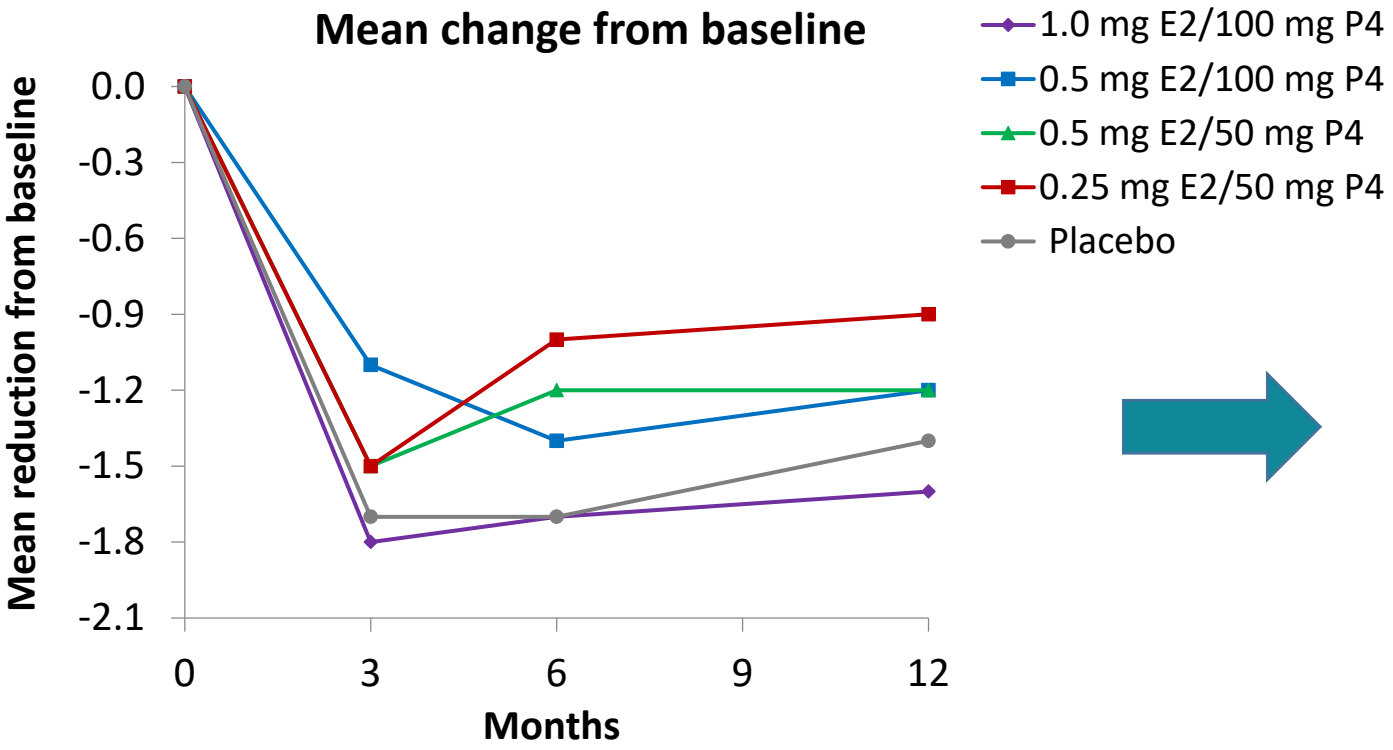


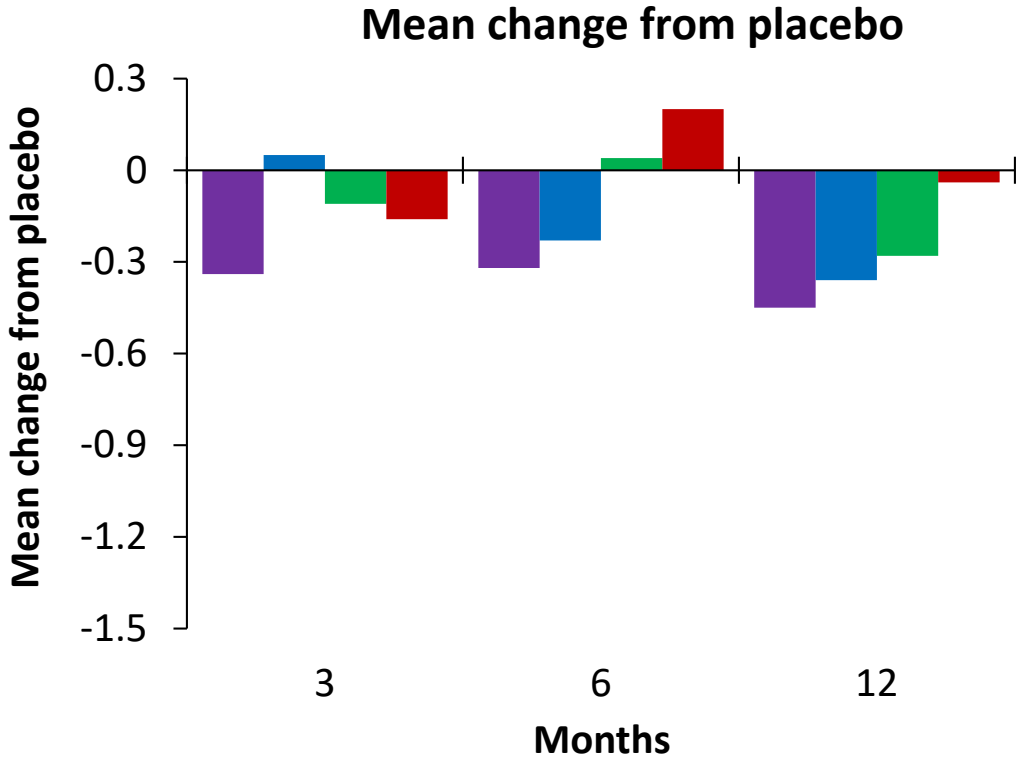
E2/P4 (mg)	1/100	0.5/100	0.5/50	0.25/50	Placebo
Population, n (%)					
MITT	416	422	421	423	151
Completed at 52 weeks	284 (68.2)	304 (71.9)	312 (74.1)	280 (66.2)	93 (61.2)

BMI: body mass index; MITT: modified intent-to-treat population.

Vaginal Dryness During Intercourse in Women <55 y

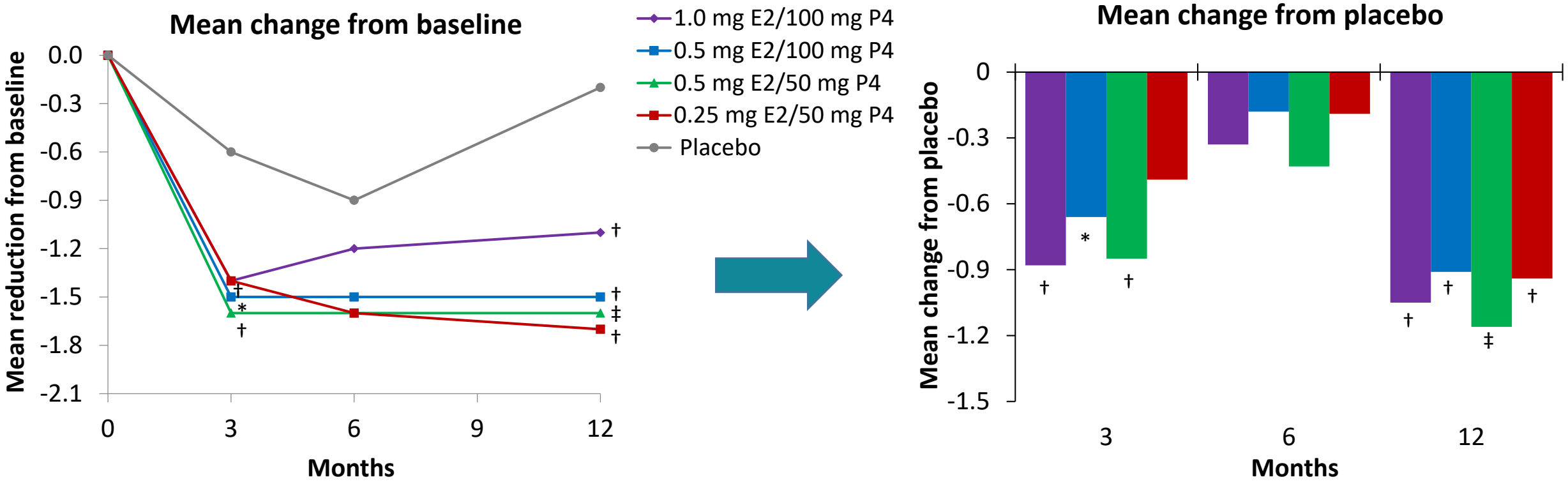
- No significant improvements between E2/P4 doses and placebo were observed
  - Mean baseline scores ranged from 3.5 to 4.5





Vaginal Dryness During Intercourse in Women ≥55 y

- Significant improvements from baseline versus placebo were seen at week 12 with the 3 highest doses and at month 12 for all E2/P4 doses
  - Mean baseline scores ranged from 3.6 to 4.0



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

Conclusions

- In women 55 years and older, vaginal dryness significantly improved during intercourse (measured by MENQOL) at week 12 (except for the lowest dose) and month 12 with E2/P4 vs placebo
- These data extend REPLENISH trial results that show the oral E2/P4 softgel capsules
  - Reduced the frequency and severity of moderate to severe hot flushes[1]
  - Improved quality of life outcomes in menopausal women with a uterus[2]
- 1 mg E2/100 mg P4 was approved by the FDA as Bijuva (October 2018) for moderate to severe VMS in women with a uterus
  - First combined bioidentical E2/P4 oral product to be approved by the FDA
  - Represents a new oral HT option for menopausal women with moderate to severe VMS and a uterus

1. Lobo RA, et al. *Obstet Gynecol* 2018;132:161-170. **2.** Simon JA, et al. *Menopause.* 2018 [Epub ahead of print, Nov 26].