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

James A Simon, MD\textsuperscript{1}; Sharon J Parish, MD\textsuperscript{2}; Brian Bernick, MD\textsuperscript{3}; Shelli Graham, PhD\textsuperscript{3}; Sebastian Mirkin, MD\textsuperscript{3}

\textsuperscript{1}George Washington University School of Medicine, IntimMedicine Specialists, Washington, DC; \textsuperscript{2}Weill Cornell Medical College, New York, NY; \textsuperscript{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\textsuperscript{1-3}
  • Symptoms can be effectively treated with HT\textsuperscript{4}
• Use of compounded bioidentical HT (estradiol [E2] and progesterone [P4]) has become highly prevalent in the US since the 2002 WHI report\textsuperscript{5}
  • An estimated 1 to 2.5 million US women use unapproved compounded products,\textsuperscript{5,6} representing up to 21 to 39 million prescriptions annually\textsuperscript{5}
  • Some compounded products may be associated with increased risks\textsuperscript{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.

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

### Key Inclusion and Exclusion Criteria

#### Inclusion

- Healthy menopausal women aged 40-65 years
- Intact uterus
- BMI ≤34 kg/m²
- VMS associated with menopause
- Acceptable endometrial biopsy results

**VMS Substudy**

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

#### Exclusion

- 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.

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\(^2\)

\[\text{Mean reduction from baseline}\]

\[\text{Week}\]

\[\text{Frequency}\]

\[\text{0} \quad \text{1} \quad 	ext{2} \quad 	ext{3} \quad 	ext{4} \quad 	ext{5} \quad 	ext{6} \quad 	ext{7} \quad 	ext{8} \quad 	ext{9} \quad 	ext{10} \quad 	ext{11} \quad 	ext{12}\]

\[\begin{array}{c}
1 \text{ mg E2/100 mg P4*} \\
0.5 \text{ mg E2/100 mg P4†} \\
0.5 \text{ mg E2/50 mg P4‡} \\
0.25 \text{ mg E2/50 mg P4*} \\
\text{Placebo}\end{array}\]

\[P<0.05 \text{ from *Weeks 3–12; †Weeks 4–12; ‡Weeks 6–12 vs placebo.}\]

\[\text{Severity}\]

\[\text{Mean reduction from baseline}\]

\[\text{Week}\]

\[\text{0} \quad \text{1} \quad 	ext{2} \quad 	ext{3} \quad 	ext{4} \quad 	ext{5} \quad 	ext{6} \quad 	ext{7} \quad 	ext{8} \quad 	ext{9} \quad 	ext{10} \quad 	ext{11} \quad 	ext{12}\]

\[\begin{array}{c}
1 \text{ mg E2/100 mg P4*} \\
0.5 \text{ mg E2/100 mg P4*} \\
0.5 \text{ mg E2/50 mg P4†} \\
0.25 \text{ mg E2/50 mg P4‡} \\
\text{Placebo}\end{array}\]

\[P<0.05 \text{ from *Weeks 3–12; †Weeks 7, 9–12; ‡Weeks 6, 7, 9 vs placebo.}\]

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)
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/m²

**Randomized to treatment**

**n=1845**

**MITT population**

**n=1833**

<table>
<thead>
<tr>
<th>E2/P4 (mg)</th>
<th>Population, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITT</td>
<td>Completed at 52 weeks</td>
</tr>
<tr>
<td>1/100</td>
<td>416</td>
</tr>
<tr>
<td>0.5/100</td>
<td>422 (71.9)</td>
</tr>
<tr>
<td>0.5/50</td>
<td>421 (74.1)</td>
</tr>
<tr>
<td>0.25/50</td>
<td>423 (66.2)</td>
</tr>
<tr>
<td>Placebo</td>
<td>151 (61.2)</td>
</tr>
</tbody>
</table>

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