Oral 17ß-Estradiol/Progesterone (E2/P4) Improved Sleep Outcomes in the REPLENISH Trial
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Introduction
• Postmenopausal women often complain about having difficulty sleeping, which has been associated with vasomotor symptoms (VMS).1
• Moderate to severe VMS can be effectively treated with approved hormone therapy (HT).2
• The phase 3 REPLENISH trial in postmenopausal women with a uterus showed that the two highest daily doses of combined E2/P4 oral HT capsules reduced frequency and severity of VMS and improved quality of life outcomes, while protecting the endometrium.3
• In October 2016, the US Food and Drug Administration (FDA) approved combined bioidentical 1 mg E2/10 mg P4 capsules as Bijuva® (TherapeuticsMD, Boca Raton, FL) for the treatment of moderate to severe vasomotor symptoms due to menopause in women with a uterus

Objective
To review the effects of E2/P4 on sleep outcomes, including pertinent data from the MENQOL study.4

Methods
Study Design
• The REPLENISH trial (NCT01942668) was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial of E2/P4 capsules in healthy postmenopausal women ≥55 years of age with moderate to severe hot flushes (≥7/day or ≥50/week) who were enrolled in the MITT substudy and randomized to daily E2/P4 (mg/mg) 1/100, 0.5/100, 0.5/50, 0.25/50 or placebo; women with fewer VMS were randomized to active E2/P4 doses only

• All subjects self-administered the MOS-Sleep5 and MENQOL6 questionnaires at baseline, week 12, and months 6 and 12

• MOS is a 12-item questionnaire measuring 6 sleep dimensions in the past 4 weeks

Results
Study Design and Demographics
• A total of 1833 women were included in the MITT population and 726 were included in the MITT 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 fewer VMS were randomized to active E2/P4 doses only

• Mean age was 55 years (40-66 years) and mean BMI was 27 kg/m2 for the MITT population; 65% were white and 32% were black

• The difficulty sleeping score significantly improved with the three highest E2/P4 doses compared with placebo at all timepoints (all, P<0.001; except for 0.5/50 at month 6) in women <55 years, significant improvements from baseline were observed with two E2/P4 doses (0.5 mg and 0.5 mg) versus placebo at all timepoints (Figure 2A)

• 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 3B)

• Incidence of somnolence was low (0.2%-1.2%) with E2/P4 versus 0% with placebo in the safety population (women who took at least one treatment capsule)

• Mediation models showed that E2/P4 had an indirect effect on sleep via VMS improvements in the MITT safety population (women who took at least one treatment capsule)

• TherapeuticsMD sponsored the study and supported the medical writing assistance provided by TherapeuticsMD, Boca Raton, FL

Conclusions
• In REPLENISH, women with VMS treated with E2/P4 capsules experienced significant and sustained improvements in sleep parameters versus placebo

• Sleep mediation models showed that E2/P4 improved moderate sleep disturbances indirectly through improvements in VMS

• In women taking oral E2/P4 capsules to treat moderate to severe VMS, E2/P4 may also improve sleep

References

Figure 1. Patient disposition

Figure 2A. Improvement in the sleep problems index II subscale and sleep disturbance subscale scores compared with placebo at all timepoints (all, P<0.001; †P<0.05; ‡P<0.01; ‡‡P≤0.001 vs placebo)

Table 1. VMS frequency and severity (n=651)

<table>
<thead>
<tr>
<th>E2/P4 (mg/mg)</th>
<th>Completed at 52 weeks</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
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<tbody>
<tr>
<td>1/100</td>
<td>284 (68.2)</td>
<td>304 (71.9)</td>
<td>280 (66.2)</td>
</tr>
<tr>
<td>0.5/100</td>
<td>200 (48.1)</td>
<td>196 (46.4)</td>
<td>196 (46.3)</td>
</tr>
<tr>
<td>0.5/50</td>
<td>141 (33.4)</td>
<td>151 (35.3)</td>
<td>154 (35.7)</td>
</tr>
<tr>
<td>0.25/50</td>
<td>227 (53.7)</td>
<td>224 (52.6)</td>
<td>200 (48.1)</td>
</tr>
<tr>
<td>Placebo</td>
<td>118 (87.4)</td>
<td>77 (51.0)</td>
<td>74 (49.0)</td>
</tr>
</tbody>
</table>

Figure 3B. Mean changes from baseline and placebo in the MENQOL difficulty sleeping item (Model 1) or VMS frequency and severity (Model 2)