E2/P4 Capsules Reduced Vasomotor Symptoms Irrespective of Age and BMI in the REPLENISH Trial
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Introduction
Vasomotor symptoms (VMS), which include hot flushes and sweats, are consistently associated with transitions through menopausal stages, and experienced by at least 50% of menopausal women. In the SWAN study, the median duration of VMS was 7.4 years.
- Administration of estrogen or estrogen/progestogen therapy to postmenopausal women significantly improves menopausal symptoms.
- REPLENISH was a phase 3 trial that evaluated the safety and efficacy of four doses of bioidentical 17βestradiol (E2)-estradiol and progesterone (E2P4, previously known as TX-01919) for treating moderate to severe VMS in menopausal women with a uterus.

Objective
To evaluate the efficacy of E2P4 for treating moderate to severe vasomotor symptoms in postmenopausal women by age and body mass index (BMI).

Methods
- REPLENISH (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial of healthy postmenopausal women (age 40 to 65 years) with a uterus seeking treatment for moderate to severe VMS.
- Co-primary efficacy endpoints of the VMS substudy were changes in frequency and severity of moderate to severe VMS from baseline at weeks 4 and 12 vs placebo. (all co-primary endpoints met).
- The 1/100 dose was approved last year as Bijuva® (TherapeuticsMD, Boca Raton, FL).

Results
- Approximately half the women were <55 years old and most (77.2%) had a BMI <30 kg/m2.
- Vasomotor symptoms (VMS), which include hot flushes and sweating, are
- Baseline frequency and severity of moderate to severe VMS were numerically higher in the <55 age group than in the ≥55 group. BMI baseline values varied across subgroups.

Table 1. Study participant age and BMI subgroup distribution

<table>
<thead>
<tr>
<th>Parameter</th>
<th>≤25</th>
<th>25-&lt;30</th>
<th>≥30</th>
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<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>367 (50.6)</td>
<td>355 (48.1)</td>
<td>330 (44.9)</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>57 (7.6)</td>
<td>64 (8.6)</td>
<td>61 (8.4)</td>
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Efficacy of E2/P4 for Treating VMS by Age and BMI

By Age
- Percent changes from baseline in frequency with E2/P4 were similar between age subgroups at weeks 4 (43%-56%, Figure 1A) and 12 (64%-78%, Figure 1B).
- Even though subgroup analyses were not powered for statistical significance, significant percent change reductions in VMS frequency were observed across subgroups with 1/100 and for most with the 0.5/100 groups vs placebo at week 12.

By BMI
- Percent changes from baseline in severity with E2/P4 were similar between BMI subgroups at weeks 4 (14%-25%) and week 12 (27%-46%).
- Larger percent reductions in VMS frequency and severity were observed with E2/P4 vs placebo, with some BMI subgroups meeting statistical significance at weeks 4 and 12 depending on dose (Figure 2B).
- Most of the BMI subgroups had significant reductions in severity and frequency with the 1/100 and 0.5/100 doses, with more significant differences observed at week 12 vs week 4.

Conclusions
- While the study was not powered to detect statistical significance when analyzed by subgroup, the two highest oral E2/P4 doses (1/100 and 0.5/100) reduced VMS frequency and severity, regardless of age or BMI.
- These subgroup analyses demonstrate a consistency of effect of E2/P4 among different age and BMI populations.

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References