Ultra-low Doses of TX-004HR (Estradiol Vaginal Insert) Improved Symptoms of Vulvar and Vaginal Atrophy while Maintaining Serum Levels of Estradiol within the Normal Postmenopausal Range

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Background
• Approximately 30M US postmenopausal women with symptomatic vulvar and vaginal atrophy (VVA) remain untreated, partly due to concerns about estrogen exposure and its perceived risks
• Vaginal, low-dose estrogens are recognized as effective treatment options for women with moderate to severe symptoms of VVA
• TX-004HR is an applicator-free, softgel vaginal insert containing ultra-low doses of estradiol (E2; 4 or 10 μg), specifically designed to minimize systemic absorption of E2 while treating symptomatic VVA
• In the REJOICE trial, women with moderate to severe dyspareunia associated with VVA had statistically significant improvements from baseline in percentages of superficial and parabasal cells, vaginal pH, and dyspareunia as well as vaginal dryness, a secondary endpoint, with TX-004HR compared with placebo over 12 weeks
• Earliest improvements were observed for (Table 1)
  • Moderate to severe dyspareunia at 2 weeks with all TX-004HR doses
  • Vaginal dryness at 2 weeks with TX-004HR 10 μg and 6 weeks with 4 μg
• No unexpected safety findings were observed through 12 weeks; no long-term safety data were collected

Table 1. Earliest statistically significant improvements with TX-004HR compared with placebo

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>TX-004HR 4 μg</th>
<th>TX-004HR 10 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of superficial cells</td>
<td>2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percentage of parabasal cells</td>
<td>2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vaginal pH</td>
<td>2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>2</td>
<td>0.026</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>6</td>
<td>0.0094</td>
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</table>

Methods
Phase 3 REJOICE Trial
• PK profiles of TX-004HR 4 μg and 10 μg were evaluated in a subset of subjects (n=54) who participated in the REJOICE trial, a phase 3, double-blind, placebo-controlled trial
• Participants were menopausal women aged (40 to 75 years; BMI ≤38 kg/m²) with symptomatic VVA and moderate to severe dyspareunia
• Treatments were self-administered vaginally, once daily, for 2 weeks and then twice weekly, for 10 weeks
• Details on sampling time and assessments are found in Table 2

Results
Phase 3 REJOICE Trial
• E2 PK parameters for TX-004HR compared with placebo are shown in Figure 1 and Table 3
• TX-004HR 10 μg was not different than placebo, with the exception of the Cmax that was higher than placebo on day 1
• Day 14 mean serum levels were lower than those on day 1
• Consistent with a <4-hour half-life, no accumulation of E2 was observed on day 14
• PK modeling of twice-weekly dosing predicted 24-hour average serum levels to be the same as those on day 14
• E2 concentrations on day 84 were similar to baseline and placebo for the two doses

Figure 1. Unadjusted mean serum estradiol concentration with TX-004HR over time

A. Day 1
B. Day 14
C. Day 84

Table 3. Unadjusted PK parameters for estradiol with TX-004HR in the REJOICE study

<table>
<thead>
<tr>
<th>Day</th>
<th>Unadjusted Mean</th>
<th>TX-004HR 4 μg (n=18)</th>
<th>TX-004HR 10 μg (n=19)</th>
<th>Placebo (n=17)</th>
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</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>AUC, pg*h/mL</td>
<td>91.7</td>
<td>138.2</td>
<td>116.6</td>
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<td>Cmax, pg/mL</td>
<td>6.5</td>
<td>10.9a</td>
<td>6.6</td>
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<tr>
<td></td>
<td>Cavg, pg/mL</td>
<td>3.9</td>
<td>5.8</td>
<td>4.9</td>
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<tr>
<td>Day 14</td>
<td>AUC, pg*h/mL</td>
<td>87.2</td>
<td>110.1</td>
<td>104.2</td>
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<tr>
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<td>Cmax, pg/mL</td>
<td>4.8</td>
<td>7.3</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>Cavg, pg/mL</td>
<td>3.6</td>
<td>4.6</td>
<td>4.3</td>
</tr>
</tbody>
</table>

References

Disclosures
Dr. Constantine consults to pharmaceutical companies including but not limited to TherapeuticsMD and has stock options with TherapeuticsMD. Dr. Shadiack and Mirkin are employees of TherapeuticsMD with stock/stock options. Dr. Inskeep consults with pharmaceutical companies including but not limited to TherapeuticsMD. Dr. Pickar is a consultant for Pfizer, Shionogi Inc, and TherapeuticsMD and has stock options with TherapeuticsMD. Dr. Bernick is an employee of TherapeuticsMD with stock/stock options and is also a Board member.

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