A 17β-Estradiol, Softgel, Vaginal Capsule Insert (TX-004HR) had an Early Onset of Action for Treating Vulvar and Vaginal Atrophy (VVA) and Moderate to Severe Dyspareunia

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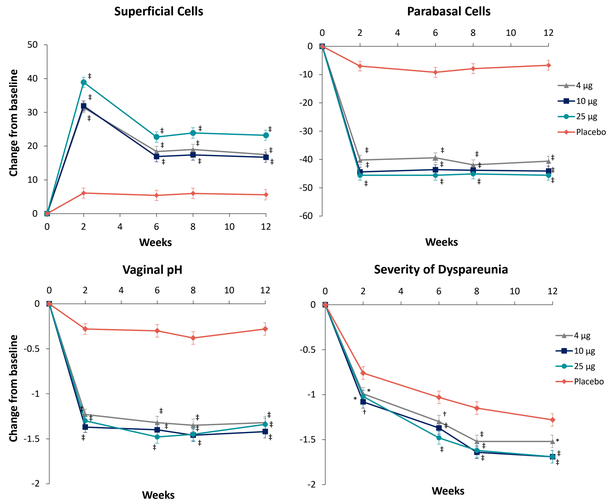
Introduction

- Dyspareunia and vaginal dryness occur in postmenopausal women as a result of the thinning, drying, and loss of elasticity of the vaginal epithelium due to reduced estrogen levels, also known as vulvar and vaginal atrophy (VVA),[1] a component of the genitourinary syndrome of menopause (GSM)[2]
- TX-004HR is a softgel vaginal insert of ultra-low–dose solubilized 17β-estradiol (E2), designed to be mucoadhesive and rapidly dissolving[3]
  - TX-004HR (IMVEXXY™ [4-µg and 10-µg doses], TherapeuticsMD, Boca Raton, FL) has recently been approved by the FDA (May 2018) for the treatment of moderate to severe dyspareunia associated with menopausal VVA
- In the phase 3 REJOICE trial (NCT02253173), the E2 vaginal insert significantly improved superficial and parabasal cell percentages, vaginal pH, and dyspareunia versus placebo in postmenopausal women with VVA and moderate to severe dyspareunia (**Figure 1**)[4]

Figure 1. Change from Baseline to Week 12 in Co-primary Endpoints



*P<0.05, †P<0.01; ‡P<0.001 for TX-004HR vs placebo.

Objective

To determine responder rates at week 2 and how week 2 findings may predict week 12 responders

Methods

Study Design

- REJOICE (NCT02253173) was a 12-week, randomized, double-blind, placebo-controlled, multicenter trial that evaluated the E2 vaginal insert in postmenopausal women (40-75 years) with VVA and a most bothersome symptom of moderate to severe dyspareunia
- Women were randomized to the E2 insert at 4 µg, 10 µg, or 25 µg, or matching placebo softgel vaginal insert once a day for 2 weeks, and then twice weekly for 10 weeks
- Co-primary efficacy endpoints analyzed for each dose were changes from baseline to week 12 compared with placebo for percentages of vaginal superficial and parabasal cells, vaginal pH, and dyspareunia severity
- Women who received treatment had baseline values for all co-primary variables and at least one post-baseline value for the co-primary variables, completed the study at 12 weeks, and were ≥80% overall study drug compliant, were included in the efficacy evaluable (EE) population

Responder Analyses

- Responder analyses reported here were performed in the EE population
- Women were defined as responders if they had ≥2 of the following:
  - Vaginal superficial cell percentage >5%
  - Vaginal pH <5.0, or
  - Improvement from baseline in dyspareunia ≥1 category (measured on a scale of 0 to 3, where 0 = no symptoms and 3 = severe)
- The proportion of responders was calculated by dividing the number of positive responders by women with available responder data
- Odds ratios (ORs) for a positive response at week 12 given a positive response at week 2 were calculated

Results

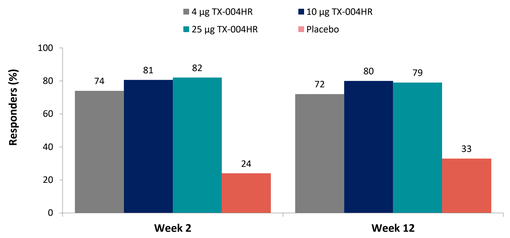
Disposition and Demographics

- 764 postmenopausal women were randomized to 4-µg (n=191), 10-µg (n=191), or 25-µg (n=190) vaginal E2 inserts, or placebo (n=192); 695 were included in the EE population
- Participants had a mean of age of 59 years and a mean BMI of 26.7 kg/m^2; the majority (87%) were white and 12% were African American

Responder Analyses

- Significantly more responders were observed with the E2 vaginal insert than with placebo at week 12 (**Figure 2**)
  - A similar pattern was observed at week 2 (significance not tested)

Figure 2. Responders with the Estradiol Vaginal Insert at Weeks 2 and 12



- Although the overall number of responders at 2 and 12 weeks are similar, the proportion of responders to all three endpoints increased significantly by 12 weeks, primarily due to improvement in the dyspareunia endpoint as observed in **Figure 1**
- The likelihood of being a responder with the E2 vaginal insert were 9- to 14-fold higher than that with placebo at week 2, and 5- to 8-fold higher at week 12 (**Table 1**)

Table 1. Odds Ratios of Responding with the Vaginal Estradiol Insert Versus Placebo

Timepoint	Odds ratio (95% CI)		
	4 µg E2	10 µg E2	25 µg E2
Week 2	8.8 (5.3–14.7)	13.7 (8.0–23.5)	14.4 (8.4–24.9)
Week 12	5.4 (3.4–8.8)	8.4 (5.1–14.0)	7.6 (4.7–12.4)

CI: confidence interval; E2: 17β-estradiol.

- When all women (independent of treatment) were analyzed in aggregate, similar percentages of responders were observed at weeks 2 and 12, respectively, with
  - All groups combined (including placebo): 65% and 66%
  - Active-treatment groups only: 80% and 78%
- Of women in active-treatment groups only who responded at week 12, 85% responded at week 2
- Being a responder at week 2 highly predicted being a responder at week 12 in the total EE population and in the active treatment groups only (**Table 2**)

Table 2. Overall Odds Ratios of a Positive Response on Week 12 Given a Positive Response on Week 2

Population	Odds ratio (95% CI)
Total	13.1 (8.8–19.7)
Active (E2) groups only	7.9 (4.7–13.2)

CI: confidence interval; E2: 17β-estradiol.

Conclusions

- A consistent effect of TX-004HR in menopausal women with moderate to severe dyspareunia was observed as early as 2 weeks of therapy as shown by the high percentage of responders
- A positive response to TX-004HR at week 2 predicted a positive response at week 12
- These data may inform clinicians counselling women with moderate to severe dyspareunia associated with menopause regarding response to the E2 vaginal insert (TX-004HR)

References

1. Mac Bride MB, et al. *Mayo Clin Proc* 2010;85:87-94. **2.** Portman DJ, et al. *Menopause* 2014;21:1063-1068. **3.** IMVEXXY™ (estradiol vaginal inserts). TherapeuticsMD. Boca Raton, FL. 2018. **4.** Constantine G, et al. *Menopause* 2017;24:409-416.

Disclosures

- Dr. Constantine consults for multiple pharmaceutical companies including but not limited to TherapeuticsMD and has stock options from TherapeuticsMD. Dr. Millheiser has served as consultant to or on the advisory boards of AMAG, Aytu BioScience, Duchesnay, ExploraMed Development, Valeant, and Willow; is a stockholder in Aytu Bioscience, Viveve, and Willow; is currently Chief Medical Officer of Sprout Pharmaceuticals. Dr. Kaunitz is serving as consultant to or on the advisory boards of AMAG Pharmaceuticals, Bayer Healthcare, Mithra, and Shionogi Inc; and has received research support (to University of FL) from Allergan, Bayer Healthcare, and TherapeuticsMD. Drs. Graham, Bernick, and Mirkin are employees of TherapeuticsMD with stock/stock options. Dr. Bernick is also a Board member of TherapeuticsMD.
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