The REJOICE Trial: A Phase 3 Randomized Controlled Trial Evaluating the Safety and Efficacy of a Novel Vaginal Estradiol Softgel Capsule for Symptomatic Vulvar and Vaginal Atrophy (VVA)

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Background
- Vulvar and vaginal atrophy (VVA) is the thinning, drying, and loss of elasticity of the vaginal epithelium associated with the loss of estrogen in menopause.
- Up to 69% of postmenopausal women show clinical signs of VVA, with roughly half reporting symptoms.
- Without treatment, VVA can be progressive and can reduce quality of life.
- Although an estimated 30 million US women remain untreated, many because of dissatisfaction with available products.
- TX-004HR (TherapeuticsMD, Inc., Boca Raton, FL) is an investigational, applicator-free, low-dose, vaginal softgel capsule containing solubilized 17α-estradiol. It is designed to provide rapid efficacy for symptoms of VVA with low systemic absorption, easy insertion, and complete dissolution to minimize discharge.
- TX-004HR with low systemic absorption, easy insertion, and complete dissolution to minimize discharge.

Objectives
- To assess the efficacy and safety of 3 doses of TX-004HR compared with placebo at 12 weeks in postmenopausal women with moderate-to-severe VVA and dyspareunia.

Methods

Study Design
- The REJOICE Trial was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study of TX-004HR 4 µg, 10 µg, and 25 µg.
- Treatments were self-administered vaginally, once daily, for 2 weeks and then twice weekly, for 10 weeks.
- Patient follow-up for all endpoints occurred at baseline, and at weeks 2, 6, 8, and 12 (Table 1).
- Questionnaires regarding satisfaction with treatment were answered by participants at the end of the study.

Study Participants
- 764 postmenopausal women were randomized to 4 µg (n=191), 10 µg (n=191), or 25 µg (n=192) vaginal E2 softgel capsules or placebo (n=192).
- Participants had a mean age of 59 years and a mean BMI of 26.7 kg/m²; the majority (87%) were white; 56% had an intact uterus.

Efficacy

Co-Primary Efficacy Endpoints (MITT Population)
- Statistically and clinically meaningful improvements were achieved with all three doses of TX-004HR for all 4 co-primary endpoints at week 12 compared with placebo (Figure 1).
- 4 µg: P=0.001 for all, except for dyspareunia, P=0.119.
- 10 µg: P=0.001 for all.
- 25 µg: P=0.001 for all.

Secondary Efficacy Endpoints (MITT Population)
- Onset of efficacy was observed at week 2 and sustained throughout the trial.
- The reductions in percentage of superficial cells increased (P=0.0001), parabasal cells decreased (P=0.0001), vaginal pH decreased (P=0.0001), and severity score for MBS of dyspareunia decreased (P=0.0010 for 10 µg; P=0.05 for 25 µg; P=0.026 for 4 µg) at week 2 with TX-004HR versus placebo.
- Benefit was sustained at weeks 6 and 8.

Safety

Adverse events (AEs) were mild to moderate in severity and not associated with discontinuation from the study.

Conclusions
- All doses of TX-004HR were safe and effective in women with VVA and moderate-to-severe dyspareunia.
- All co-primary efficacy endpoints statistically improved from baseline versus placebo with all doses.
- All improvements were clinically meaningful.
- Onset of effect was seen as early as 2 weeks and was maintained throughout the study for the 4 co-primary endpoints (percentages of superficial and parabasal cells, vaginal pH, and dyspareunia).
- Vaginal dryness significantly improved throughout the study.
- Vaginal itching or irritation improved by week 2 with 10 µg TX-004HR (69% to 76%) versus placebo (57%).
- No clinically significant differences in AEs were observed between treatment and placebo groups.

References

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