Rejoice Trial: Evaluation of an Applicator-Free Vaginal Estradiol Softgel Capsule for the Treatment of Postmenopausal Dyspareunia Associated With 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 menopausal decline in endogenous estrogen production,[1] which may be progressive without treatment[2]
- Up to 69% of postmenopausal women have clinical signs of VVA,[3] and nearly half suffer from symptoms associated with VVA, including dyspareunia, vaginal dryness, irritation, and itching[4]
  - VVA can significantly impair a woman's quality of life[5]
- Systemic or local estrogens are effective therapies, but women are generally dissatisfied with currently available treatment options[6]
- TX-004HR (TherapeuticsMD, Inc., Boca Raton, FL) is an investigational, applicator-free, vaginal softgel capsule containing 17β-estradiol (E2) designed to be efficacious for the treatment of menopausal VVA signs and symptoms with lower systemic exposure, rapid onset of action, improved efficacy and user experience, with a new lower effective dose (4 µg).
  - Estradiol is released into the vagina on contact of the softgel capsule with the vaginal mucosa, and does not require vaginal secretions to activate the formulation. Complete dissolution has been reported, minimizing vaginal discharge
- Phase 1 studies demonstrated lower systemic estrogen concentrations compared with an approved low-dose vaginal estradiol tablet at 10 µg and 25 µg doses,[7] and a phase 2 study showed significant improvement in the clinical signs of VVA with this softgel capsule compared with placebo[8]

Objective

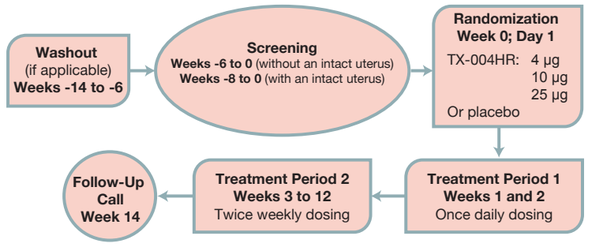
- To assess the safety and efficacy of 3 doses of TX-004HR (4 µg, 10 µg, and 25 µg) in postmenopausal women with moderate-to-severe symptoms of VVA

Methods

Study Design

- The REJOICE Trial was a pivotal, randomized, double-blind, placebo-controlled, 12-week, phase 3 clinical trial conducted at 89 sites across the United States and Canada
- Women were randomly assigned to receive either 4 µg, 10 µg, or 25 µg of TX-004HR, or placebo (Figure 1)

Figure 1. Schematic of Study Design



- Treatments were administered vaginally once daily for 2 weeks and then twice weekly (~3 to 4 days apart) for 10 weeks (Figure 1)

Patient Population

- Postmenopausal women were enrolled if they met the following criteria:
  - Were age 40 to 75 years, with body mass index ≤38 kg/m^2
  - Had ≤5% superficial cells on vaginal cytological smear
  - Had a vaginal pH >5.0
  - Self-reported a most bothersome symptom (MBS) of moderate-to-severe vaginal pain associated with sexual activity (dyspareunia)
- Exclusion criteria were consistent with other vaginal estradiol therapy studies

Co-primary, Key Secondary, and Safety Endpoints

Table 1. Study Endpoints

Parameter	Endpoints
Co-primary Change from baseline to week 12 in:	Percentage of vaginal superficial cells Percentage of vaginal parabasal cells Vaginal pH Severity of the most bothersome symptom (MBS) of dyspareunia
Key secondary	Vaginal dryness
Safety	Vital signs Lab tests Physical and gynecological examinations Endometrial biopsies Adverse events (AEs)

Analyses

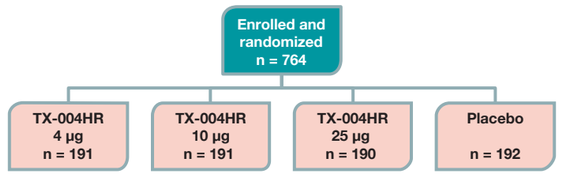
- Pairwise comparisons were performed for change from baseline to week 12 in each of the endpoints using ANCOVA for each dose of TX-004HR (4 µg, 10 µg, 25 µg) vs placebo

Results

Disposition of Study Participants

- 764 postmenopausal women (mean age 59 years) were randomized (Figure 2)

Figure 2. Disposition of Study Groups (Safety Population)



Efficacy Endpoints (MITT Population, n = 747)

- All 4 co-primary endpoints significantly improved with all 3 doses of TX-004HR compared with placebo (Table 2)
- Vaginal dryness significantly improved with all 3 doses of TX-004HR compared with placebo (Table 2)

Table 2. Statistical Significance of Results

Endpoints	Effect of TX-004HR (all doses) vs placebo	Doses of TX-004HR *P*-values*		
		4 µg n = 186	10 µg n = 188	25 µg n = 186
Superficial cells	Increased	<0.0001	<0.0001	<0.0001
Parabasal cells	Decreased	<0.0001	<0.0001	<0.0001
Vaginal pH	Decreased	<0.0001	<0.0001	<0.0001
Severity of dyspareunia	Improved	0.0149	<0.0001	<0.0001
Severity of vaginal dryness	Improved	0.0014	<0.0001	<0.0001

*Based on mean change from baseline to week 12 compared with placebo (n = 187)

Safety

- TX-004HR was well tolerated
- No clinically significant differences in AEs were observed between treatment and placebo groups
- No treatment-related serious AEs were reported

Conclusions

- In the REJOICE trial, TX-004HR met all pre-specified co-primary endpoints
  - Percentage of superficial cells
  - Percentage of parabasal cells
  - Vaginal pH
  - MBS of dyspareunia
- In addition, TX-004HR significantly improved the key secondary endpoint of vaginal dryness
- TX-004HR was safe and well tolerated in this clinical trial of postmenopausal women with VVA
- Further detailed analyses are ongoing

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Disclosures

GC and HK consult to pharmaceutical companies including but not limited to TherapeuticsMD. BB, SG, and SM are employees of TherapeuticsMD. TherapeuticsMD sponsored the study and supported the medical writing assistance provided by Jolene Mason, PhD (Precise Publications, LLC).

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Presented at the 2016 ISSWSH Annual Meeting, February 25-28, 2016, Charleston, SC.