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)

LBSAT-12

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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[1]
  - Up to 69% of postmenopausal women show clinical signs of VVA,[2] with roughly half reporting symptoms[3,4]
  - Without treatment, VVA can be progressive[5] and can reduce quality of life.[6] However, an estimated 30 million US women remain untreated,[4,7,8] many because of dissatisfaction with available products[7]
- TX-004HR (TherapeuticsMD, Inc., Boca Raton, FL) is an investigational, applicator-free, low-dose, vaginal softgel capsule containing solubilized 17β-estradiol. It is designed to provide rapid efficacy for symptoms of VVA with low systemic absorption, easy insertion, and complete dissolution to minimize discharge
  - Phase 1 studies showed that systemic estrogen concentrations with 10 µg and 25 µg TX-004HR were 2-3 times lower than the levels observed with an approved low-dose vaginal estradiol tablet[9]

Objective

- 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

Table 1. Study Endpoints

Parameter	Endpoints
Efficacy **Co-primary** Mean 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
Secondary Mean change from baseline to weeks 2, 6, and 8 in:	• Percentage of vaginal superficial cells • Percentage of vaginal parabasal cells • Vaginal pH • Severity of the most bothersome symptom (MBS) of dyspareunia
Mean change from baseline to weeks 2, 6, 8, and 12 in:	• Severity of vaginal dryness • Severity of vulvar and/or vaginal itching or irritation
Safety	• Vital signs • Routine laboratory tests • Physical and gynecological examinations • Pap smears and endometrial biopsies • Adverse events (AEs)

Study Participants

- Postmenopausal women (40-75 years) were included if they had:
  - VVA defined as ≤5% superficial cells on vaginal cytological smear; vaginal pH >5.0
  - Self-identified their most bothersome VVA symptom (MBS) as moderate-to-severe dyspareunia
  - Body mass index ≤38 kg/m^2
  - Anticipated sexual activity (with vaginal penetration) during the trial period
- Exclusion criteria were typical for those of estrogen VVA studies[10-12] and are consistent with the FDA guidelines[13]
- Use of oral estrogen-, progestin-, androgen-, or SERM-containing drug products were prohibited within 8 weeks of study start

Statistical Analyses

- ANCOVAs based on mixed model repeated measures using baseline and age as covariates with random intercept were used to compare change from baseline with placebo in each of the endpoints for each dose of TX-004HR

Results

Study Participant Disposition and Demographics

- 764 postmenopausal women were randomized to 4 µg (n=191), 10 µg (n=191), or 25 µg (n=190) vaginal E2 softgel capsules or placebo (n=192)
- Participants had a mean age of 59 years and a mean BMI of 26.7 kg/m^2; the majority (87%) were white; 56% had an intact uterus

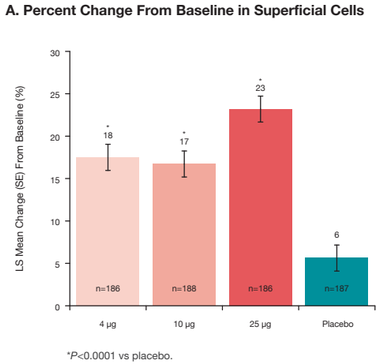
Co-Primary Efficacy Endpoints (MITT Population)

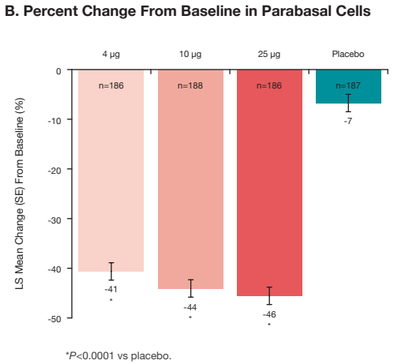
- Statistically and clinically meaningful improvements were achieved with all three doses of TX-004HR for all 4 co-primary endpoints at week 12 compared with placebo (Figure 1):
  - 4 µg: *P*<0.0001 for all, except for dyspareunia, *P*=0.0149
  - 10 µg: *P*<0.0001 for all
  - 25 µg: *P*<0.0001 for all

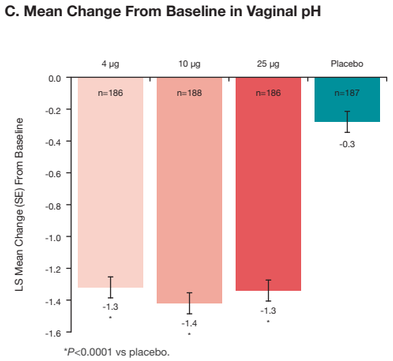
Secondary Endpoints (MITT Population)

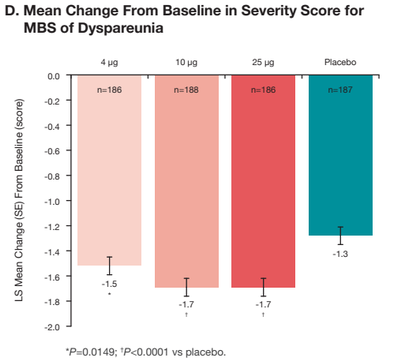
- Onset of efficacy was observed at week 2 and sustained throughout the trial
  - The percentages of superficial cells increased (*P*<0.0001), parabasal cells decreased (*P*<0.0001), vaginal pH decreased (*P*<0.0001), and severity score for MBS of dyspareunia decreased (*P*<0.01 for 10 µg; *P*<0.05 for 25 µg; *P*=0.026 for 4 µg) at week 2 with TX-004HR versus placebo
  - Benefit was sustained at weeks 6 and 8

Figure 1. Change From Baseline in the Four Co-Primary Endpoints at Week 12 (MITT Population; n=747)









- Vaginal dryness and vulvar and/or vaginal itching or irritation:
  - 93% reported moderate-to-severe vaginal dryness at baseline
  - Statistically and clinically meaningful improvements were observed throughout the study for:
    - Vaginal dryness with all doses at all time points, except 4 µg at 2 weeks (*P*=0.1269) (Figure 2A)
    - Vulvar and/or vaginal itching or irritation at weeks 8 and 12 for 10 µg (*P*=0.0356 and *P*=0.0055, respectively) and for 25 µg at week 12 (*P*=0.0263; Figure 2B)

Product Acceptability

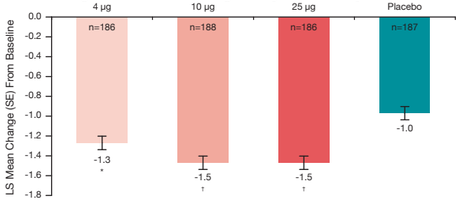
- Most of the women found the product easy to use (89%) and ease of insertion good to excellent (80%)
- Most women were satisfied or very satisfied with TX-004HR (69% to 76%) versus placebo (57%)
- Of the women who used a different product previously, the majority using TX-004HR (62% to 71% versus 52% for placebo) preferred it over their previous product

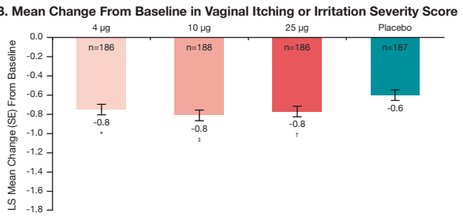
Safety Endpoints (Safety Population)

- TX-004HR was well tolerated
- For drug-related, treatment-emergent AEs (in ≥3% of women within any group)
  - Headache was reported numerically more with TX-004HR than with placebo
  - Vaginal discharge, nasopharyngitis, and vulvovaginal pruritus were reported numerically less with TX-004HR versus placebo
- No clinically significant differences in AEs were observed between treatment and placebo groups
- No signal of estrogenic stimulation of the endometrium
  - No cases of endometrial hyperplasia or malignancies were reported
- No treatment-related serious AEs or deaths were reported

Poster presented at the 2016 ENDO Annual Meeting, April 1–4, Boston, MA.

Figure 2. Change From Baseline in Secondary Endpoints at Week 12 (MITT Population; n=747)





Conclusions

- All doses of TX-004HR were safe and effective in women with VVA and moderate-to-severe dyspareunia
  - All 4 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 8 with 10 µg TX-004HR; by week 12 for 4 µg (*P*=0.0503) and 25 µg
- Although head-to-head trials were not performed, TX-004HR had similar reductions in severity score for dyspareunia (-1.5 to -1.7) to products currently approved for the treatment of VVA and/or dyspareunia (-1.2 to -1.6)[14-16]
- TX-004HR was safe and well tolerated in this clinical trial in postmenopausal women with VVA
- TX-004HR can treat the clinical signs and symptoms of VVA with negligible to very low systemic absorption (PK substudy companion poster presented Friday, April 1, 2016)
- TX-004HR may be a new therapy for VVA, a common but undertreated condition

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Disclosures

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