TX-004HR Provided Robust Improvement of Symptomatic Postmenopausal Vulvar and Vaginal Atrophy (VVA) with Negligible to Very Low Systemic Absorption of Estradiol: Results of Phase 1 and 3 Clinical Trials

Sharon J Parish, MD; Lisa Larkin, MD; James A Simon, MD; Brian Bernick, MD; Sebastian Mirkin, MD

Weill Cornell Medicine, White Plains, NY; Lisa Larkin MD and Associates, Marlemount, OH; IntiMedicine Specialists, Washington, DC; TherapeuticsMD, Boca Raton, FL

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.\(^2\)
- TX-004HR (ultra-low doses of solubilized 17β-estradiol [E2]; 4, 10 or 25 µg, softgel vaginal insert) was designed to rapidly treat VVA symptoms without increasing systemic E2, to be easily inserted without an applicator, and to completely dissolve to minimize discharge.\(^3\)

Objective
- To review TX-004HR phase 3 data showing improvements in menopausal VVA symptoms and phase 1 and 3 evidence of negligible to very low systemic E2 absorption.

Methods

**REJOICE Trial**
- The REJOICE trial was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study of TX-004HR 4 µg, 10 µg, and 25 µg compared with placebo.
- Participants were menopausal women aged 40 to 75 years; BMI ≤70 kg/m² with symptomatic VVA and a history of moderate to severe dyspareunia.
- Treatments were self-administered once daily for 2 weeks, then twice weekly for 10 weeks.
- Safety endpoints included endometrial histology and adverse events (AEs).

**Phase 1 and 3 PK Data**
- Systemic E2 levels (n=72) 4 µg and 10 µg TX-004HR were similar to placebo on days 1 and 14, and at all time points (Figure 3).
- See poster by Goldfarb et al for all PK parameters (TX-004HR PK)
- TX-004HR 4 µg had no significant differences from placebo in E2 PK parameters
- PK with TX-004HR 10 µg was not different than with placebo, with the exception of the Cmax that was higher than placebo on day 1
- TX-004HR 25 µg was associated with higher Cmax and AUC0-24, versus placebo on days 1 and 14
- E2 concentrations on day 84 were similar to baseline and placebo for the three doses

**Bioavailability Studies**
- TX-004HR PK was evaluated in two phase 1 randomized, single-dose, open-label, 2-way crossover studies (N=36 for each).
- Participants were menopausal women aged 40 to 75 years; BMI ≤70 kg/m² with symptomatic VVA and a history of moderate to severe dyspareunia.
- Participants were healthy menopausal women aged 40-65 years; BMI 18.5 to 30.0 kg/m².
- Women sequentially received a single dose of TX-004HR or a vaginal estradiol tablet depending on randomization.
- Details on sampling time and assessments are found in Table 1.

**Results**

**Phase 3 Efficacy Data (REJOICE)**
- 764 menopausal women were randomized to 4 µg (n=191), 10 µg (n=191), 25 µg (n=190) TX-004HR softgel insert or placebo (n=192).
- All TX-004HR doses were associated with improvement of the vaginal maturation index, vaginal pH, and dyspareunia at weeks 2-12 (Figure 1), and vaginal dryness (Figure 2) at weeks 6-12.
- Early improvements for moderate to severe dyspareunia were at 2 weeks with all TX-004HR doses, and for vaginal dryness at 2 weeks with TX-004HR 10 µg and 25 µg, and 6 weeks with 4 µg.
- No unexpected safety findings were observed through 12 weeks.
- Incidence of vaginal-related AEs, including vaginal discharge, was similar to placebo.
- No long-term safety data were collected.

**Conclusions**
- In the phase 3 REJOICE trial, TX-004HR improved signs and symptoms of VVA as early as 2 weeks with TX-004HR 4 µg, 10 µg, and 25 µg with negligible to very low systemic E2 absorption.
- TX-004HR provides lower systemic E2 levels than equivalent doses of an approved vaginal E2 tablet in phase 1 studies.

**References**
- Goldfarb et al. For all detailed data (TX-004HR PK).\(^1\)

**Disclosures**
- Dr. Parish is a member of advisory boards for AMAG, Allergan, and Duchesnay; is a consultant for Strategic Scientific Technologies (SST); Dr. Simon is a consultant for Strategic Scientific Technologies (SST); and AHC/Endocrine. TherapeuticsMD, Azure Biotech, Millendo Therapeutics, Pinea, Ruiyi Health, Regeneron, Sanofi, Sirtex, Salix, Salix, Sirtex, Silverline, TherapeuticsMD, Therapeutic Medical Inc.
- Dr. Bernick is an employee of TherapeuticsMD with stock/stock options.
- Dr. Mirkin is an employee of TherapeuticsMD with stock/stock options, and is also a Board member.
- Dr. Parish is a member of advisory boards for AMAG, Allergan, and Duchesnay; is a consultant for Strategic Scientific Technologies (SST).
- Dr. Parish is also a member of the editorial board of *Menopause, Andrology, and Sexual Medicine*. There are no other financial disclosures.

**Figure 1.** REJOICE trial: Change in co-primary endpoints over time from baseline to week 12

**Figure 2.** REJOICE trial: Change in dryness (secondary endpoint) over time from baseline to week 12

**Figure 3.** REJOICE trial: Unadjusted mean serum estradiol concentration with TX-004HR on days 1, 14 and 84

**Table 1.** PK Methodology for the REJOICE and bioavailability studies

**Figure 4.** Bioavailability studies: Baseline-adjusted mean plasma concentration vs time for estradiol with TX-004HR and vaginal estradiol tablet

**Table 2.** PK Parameters for the REJOICE and bioavailability studies

**Table 3.** PK Methodology for the REJOICE and bioavailability studies

**Table 4.** PK Methodology for the REJOICE and bioavailability studies

**Figure 5.** Bioavailability studies: Baseline-adjusted mean plasma concentration vs time for estradiol with TX-004HR and vaginal estradiol tablet

**Figure 6.** Bioavailability studies: Baseline-adjusted mean plasma concentration vs time for estradiol with TX-004HR and vaginal estradiol tablet

**Figure 7.** Bioavailability studies: Baseline-adjusted mean plasma concentration vs time for estradiol with TX-004HR and vaginal estradiol tablet