# Improvement in Postmenopausal Sexual Dysfunction with TX-004HR as Measured by FSFI

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## Introduction

- Vulvar and vaginal atrophy (VVA) is a chronic, progressive condition associated with the loss of estrogen in menopause[1]
  - VVA affects up to 69% of postmenopausal women[2] and clinically manifests as symptoms of vaginal dryness, irritation, dysuria, and pain (dyspareunia) or bleeding with sexual activity,[3] which can negatively affect female sexual function[4-6]
    - VVA symptoms interfere with sexual activity and satisfaction[4,5]
    - Women with female sexual dysfunction (FSD) are almost 4 times more likely to have VVA than those without FSD[6]
- TX-004HR (TherapeuticsMD, Inc., Boca Raton, FL) is an investigational, applicator-free, low-dose, vaginal softgel capsule containing solubilized 17β-estradiol
  - The vaginal capsule for TX-004HR and placebo was formulated with >90% Miglyol, a fractionated coconut oil
- The phase 3 REJOICE Trial recently demonstrated TX-004HR to be clinically efficacious and safe for treating moderate-to-severe VVA and symptoms of dyspareunia, vaginal dryness, and vulvar and/or vaginal itching or irritation[7]

## Purpose

- To assess FSD in postmenopausal women with VVA and moderate-to-severe dyspareunia following treatment with TX-004HR (at doses of 4 µg, 10 µg, and 25 µg) or placebo for 12 weeks

## Methods

### Study Design

- The REJOICE Trial was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study
- Treatments were self-administered vaginally, once daily, for 2 weeks and then twice weekly, for 10 weeks
- FSD was evaluated using the multidimensional Female Sexual Function Index (FSFI) at baseline and at week 12. The FSFI:
  - Is a brief, validated, self-reporting questionnaire consisting of 19 questions designed to assess the areas of arousal, desire, orgasm, lubrication, and pain[8]
  - Defines sexual dysfunction by a total FSFI score (the sum of the individual domain scores) of ≤26.55 out of a possible maximum score of 36[9]

### Study Participants

- Postmenopausal women (40-75 years ; BMI ≤38 kg/m$^2$) were included if they had:
  - ≤5% superficial cells on vaginal cytological smear; vaginal pH >5.0
  - Self-identified most bothersome symptom (MBS) of moderate-to-severe dyspareunia
  - Anticipated sexual activity (with vaginal penetration) during the trial period
- VVA treatments, including vaginal lubricants and moisturizers, were discontinued within 7 days prior to screening
- Use of oral estrogen-, progestin-, androgen-, or SERM-containing drug products were prohibited within 8 weeks of study start

### Statistical Analyses

- Changes from baseline in total and individual domain FSFI scores for each dose of TX-004HR were compared with placebo using ANCOVA with baseline as a covariate

## 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)
- Majority of the women were white (87%) with a mean age of 59 years and a mean BMI of 26.7 kg/m$^2$ (Table 1)
- FSFI questionnaire was completed by those who were not in the PK sub-study (n=692; 90.6%)
- Average baseline total FSFI score of 14.8 for all women indicates FSD

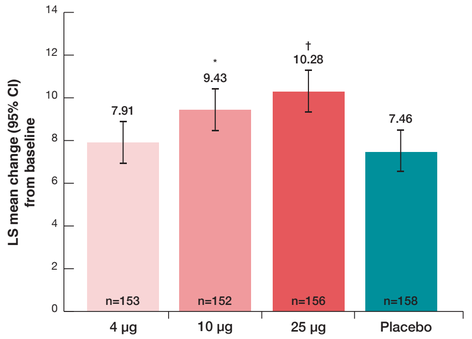
**Table 1. Demographic and Baseline characteristics in the MITT population (N=764)**

| | TX-004HR 4 µg (n=186) | TX-004HR 10 µg (n=188) | TX-004HR 25 µg (n=186) | Placebo (n=187) |
|---|---|---|---|---|
| Age, years Mean±SD | 59.8±6.0 | 58.6±6.3 | 58.8±6.2 | 59.4±6.0 |
| Race, n (%) White Black or African American Asian | 162 (87.1) 20 (10.8) 3 (1.6) | 165 (87.8) 21 (11.2) 2 (1.1) | 161 (86.6) 24 (12.9) 1 (0.5) | 160 (85.6) 21 (11.2) 1 (0.5) |
| BMI, kg/m$^2$ Mean±SD | 26.6±4.9 | 26.8±4.7 | 26.9±4.8 | 26.6±4.6 |
| Baseline total FSFI Score Mean±SD | 14.8±6.13 | 15.8±6.24 | 14.2±6.21 | 14.4±6.61 |
| Baseline FSFI Pain Score Mean±SD | 1.6±1.11 | 1.8±1.22 | 1.7±1.17 | 1.7±1.20 |

### Total FSFI Score

- After 12 weeks, total FSFI scores numerically improved from baseline in all groups, including placebo
- Total FSFI score significantly increased with 10 µg ($P$<0.05) and 25 µg ($P$=0.0019) TX-004HR versus placebo (Figure 1)

**Figure 1. Mean change from baseline in Total FSFI score at Week 12**




*$P$<0.05; †$P$=0.0019 vs placebo.

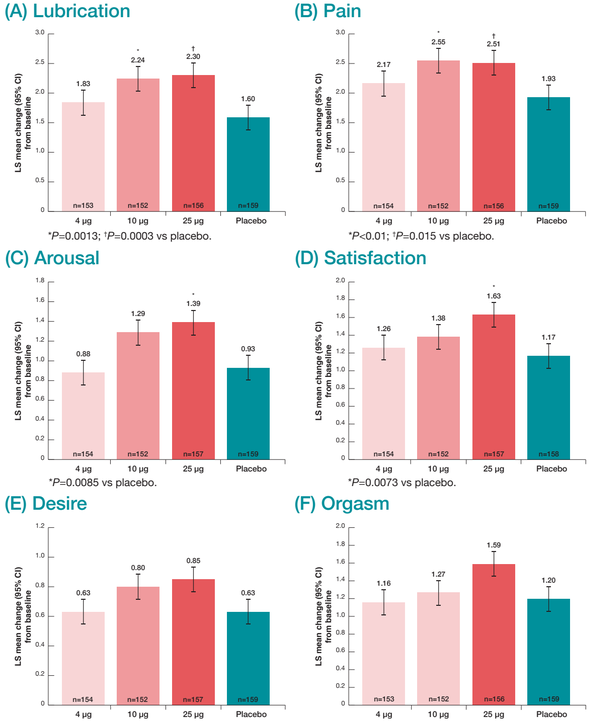
### FSFI Domain Scores

- FSFI lubrication and pain domain scores improved numerically in all groups including placebo from baseline to 12 weeks; improvements with 10 µg and 25 µg TX-004HR were statistically significantly greater than with placebo (Figure 2)
- 25 µg TX-004HR significantly improved FSFI arousal ($P$=0.0085) and satisfaction ($P$=0.0073) domain scores at 12 weeks (Figure 2)
- All 3 TX-004HR doses were comparable to placebo in their effect on the FSFI domains of desire and orgasm (Figure 2)

## Conclusions and Clinical Implications

- TX-004HR (10 µg and 25 µg) had a significantly greater effect on total FSFI score and the majority of the FSFI domain scores compared with placebo
- The large placebo response observed here could be attributed to the coconut oil (Miglyol) in the formulation for the placebo and TX-004HR, which may also contribute to the benefit of TX-004HR if it is approved
- Improvements in pain and lubrication scores support the results of the main trial, where severity of the VVA symptoms of dyspareunia and vaginal dryness improved with all doses of TX-004HR
  - Improvements in VVA symptoms may be attributed to an improvement in vaginal physiology as seen in the main study within 2 weeks of treatment with TX-004HR
- While head-to-head comparisons were not conducted, the observed increase in FSFI scores with TX-004HR (and placebo) were consistent with meaningful changes reported in ospemifene and flibanserin studies[10,11]
- With improvements in overall female sexual functioning, TX-004HR may be a promising new option for treating women with postmenopausal VVA and FSD

**Figure 2. Mean change from baseline to week 12 in the individual FSFI domain scores**




*$P$=0.0013; †$P$=0.0003 vs placebo.

*$P$<0.01; †$P$=0.015 vs placebo.

*$P$=0.0085 vs placebo.

*$P$=0.0073 vs placebo.

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### Disclosures

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

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