

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

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**Character limit 2000; now 1989**

**Objective:** TX-004HR (an investigational, solubilized 17 $\beta$ -estradiol [E2], muco-adhesive, softgel, vaginal capsule) was designed to rapidly treat VVA symptoms without increasing systemic E2, provide easy insertion without the need of an applicator, and completely dissolve to minimize discharge. The objective of this review was to present data showing improvements in menopausal VVA symptoms and negligible systemic E2 absorption with TX-004HR.

**Design:** The REJOICE trial was a randomized, double-blind, placebo-controlled, phase 3 study of TX-004HR 4  $\mu$ g, 10  $\mu$ g, and 25  $\mu$ g in menopausal women with a most bothersome symptom of moderate-to-severe dyspareunia. Treatments were self-administered once daily for 2 weeks, then twice weekly for 10 weeks. Efficacy/safety endpoints and pharmacokinetic parameters (PK substudy) of TX-004HR were compared with placebo. Two single-dose, 2-way crossover, relative bioavailability trials compared the PK of TX-004HR with a vaginal E2 tablet (10  $\mu$ g and 25  $\mu$ g).

**Results:** All TX-004HR doses vs placebo (n=747) significantly improved the vaginal maturation index, vaginal pH, and dyspareunia (primary endpoints) at weeks 2-12, and vaginal dryness (secondary) at weeks 6-12; and were well-tolerated with no reported treatment-related, serious adverse events (AEs). Incidence of vaginal-related AEs, including vaginal discharge, was similar to placebo. Systemic E2 levels (n=72) for 4  $\mu$ g and 10  $\mu$ g TX-004HR were similar to placebo on days 1 and 14, and at day 84 (no systemic E2 accumulation). Phase 1 studies (n=36 in each) showed significantly lower E2 absorption with TX-004HR 10  $\mu$ g and 25  $\mu$ g than with an approved vaginal E2 tablet at identical doses (AUC less than 1/3 of the approved product).

**Conclusion:** TX-004HR provided robust symptomatic VVA improvement as early as 2 weeks, with TX-004HR 4  $\mu$ g and 10  $\mu$ g having negligible systemic E2 absorption. TX-004HR also provided lower systemic E2 levels than equivalent doses of an approved vaginal E2 tablet.