

Ultra-low Doses of TX-004HR (Estradiol Vaginal Softgel Capsule) Improve Symptoms of Vulvar and Vaginal Atrophy while Maintaining Serum Levels of Estradiol within the Normal Postmenopausal Range

Ginger D Constantine, MD¹; Annette M Shadiack, PhD²; Philip B Inskeep, PhD³; James H Pickar, MD⁴, Brian Bernick, MD²; Sebastian Mirkin, MD²

¹EndoRheum Consultants, LLC, Malvern, PA; ²TherapeuticsMD, Boca Raton, FL;

³InskeepDMPK, LLC, East Lyme, CT; ⁴Columbia University Medical Center, New York, NY;

IMS 2018 (deadline January 12, 2018)

Character limit: 2000, now 1983

Objective: TX-004HR, an investigational, vaginal, softgel capsule of soluble 17 β -estradiol (E2), is being developed to treat menopausal vulvar and vaginal atrophy (VVA). Many women with VVA remain untreated due to concerns of estrogen exposure. Serum E2 levels following TX-004HR, which significantly reduced moderate-to-severe VVA symptoms (dyspareunia [primary endpoint]/vaginal dryness [secondary]), were determined and compared with that of the normal postmenopausal range (9.3 ng/mL).

Methods: A 12-week, randomized, placebo-controlled, phase 3, safety/efficacy study (REJOICE) was conducted in menopausal women with VVA. TX-004HR (4 or 10 μ g) was administered daily for 14 days, then twice weekly for 10 weeks. Serum E2 levels using validated GC-MS/MS and pharmacokinetics (PK) were determined in 17-19 subjects/group (mean BMI 28.2 kg/m²) on days 1 and 14 of daily dosing and day 84 of twice-weekly maintenance dosing.

Results: The day 1, 0h, mean \pm SD, serum E2 level was 4.05 \pm 2.69 pg/mL (95th percentile 8.49 pg/mL; max 17.2 pg/mL). The mean 24-hour average levels on day 1 for the placebo, 4 μ g, and 10 μ g groups were 4.86 \pm 3.22, 3.92 \pm 1.46, and 5.76 \pm 3.13 pg/mL, respectively. Day 14 mean serum levels were lower than those on day 1; 4.34 \pm 2.77, 3.63 \pm 1.78, and 4.59 \pm 2.27 pg/mL, respectively. With a <4-hour half-life, no accumulation of E2 was observed on day 14. PK modeling of twice-weekly dosing predicted 24-hour average serum levels to be the same as those on day 14. On day 84 (maintenance phase), serum E2 levels were 4.36, 4.25, and 4.79 pg/mL, respectively.

Conclusions: The TX-004HR soluble E2, softgel-capsule, twice-weekly regimen maintained VVA symptom improvement, while maintaining serum E2 levels within the normal postmenopausal range. Lower serum E2 levels on day 14 vs day 1 suggest vaginal wall regeneration and/or improvement in vaginal cell metabolic activity. These findings are relevant given the progressive nature of VVA, which requires chronic treatment.