Symptomatic Vulvar and Vaginal Atrophy (VVA) Relief was Achieved with Negligible to Very Low Systemic Absorption of Estradiol with TX-004HR (Estradiol Vaginal Insert): PK Comparison to Systemic and a Vaginal Estradiol

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Background

- Greater than 60% of postmenopausal breast cancer patients report experiencing symptoms of vulvar and vaginal atrophy (VVA) including vaginal dryness and dyspareunia.[1,2]
- VVA symptoms are reported as the most poorly addressed of their side effects while on adjuvant endocrine therapy including aromatase inhibitors.[3]
  - Up to 30% of women discontinue aromatase inhibitors due to adverse effects.[4]
- Local estrogen therapy is a treatment of VVA in postmenopausal women; however, a major concern of prescribing local estrogen therapy in breast cancer patients is the potential risk of systemic absorption and potential breast effects.[3]
  - The American Congress of Obstetricians and Gynecologists,[5] among others,[6,7] supports the use of low-dose vaginal estrogen in women with a history of estrogen-dependent breast cancer who are experiencing urogenital symptoms and are unresponsive to nonhormonal remedies.
- TX-004HR is an applicator-free, vaginal softgel insert containing an ultra-low dose of estradiol (E2), specifically designed to minimize systemic absorption of E2 while treating symptomatic VVA.[8]
- In the REJOICE trial, women with moderate to severe dyspareunia associated with VVA had statistically significant improvements from baseline in percentages of superficial and parabasal cells, vaginal pH, and dyspareunia as well as vaginal dryness, a secondary endpoint, with TX-004HR compared with placebo over 12 weeks.
  - No unexpected safety findings were observed through 12 weeks; no long-term safety data were collected.
  - See poster by Parish et al for overview of the REJOICE trial.

Objective

- Compare the pharmacokinetic (PK) profiles of currently available low-dose oral E2 products with TX-004HR for the treatment of postmenopausal VVA

Methods

***Bioavailability Studies*[9]**

- TX-004HR PK was evaluated in two phase 1, randomized, single-dose, open-label, 2-way crossover studies (N=36 for each)
  - TX-004HR 10 µg and 25 µg were compared with vaginal E2 tablet 10 µg and 25 µg (Vagifem®; Novo Nordisk, Plainsboro, NJ), respectively
- Enrolled participants were healthy postmenopausal women aged 40-65 years with BMI 18.5 to 30.0 kg/m^2
- Women sequentially received a single dose of TX-004HR and vaginal E2 tablet depending on randomization
- Details on sampling time and assessments are found in **Table 1**

***Phase 3 REJOICE Trial*[8]**

- PK profiles of TX-004HR 4 µg, 10 µg and 25 µg were evaluated in a subset of subjects (n=72) who participated in the REJOICE trial, a phase 3, double-blind, placebo-controlled trial
- Enrolled participants were postmenopausal women aged 40 to 75 years, BMI ≤38 kg/m^2, with symptomatic VVA and moderate to severe dyspareunia
- Treatments were self-administered vaginally, once daily, for 2 weeks and then twice weekly, for 10 weeks
- Details on sampling time and assessments are found in **Table 1**

Table 1. Methodology for bioavailability and phase 3 studies

Estradiol Assessment	Bioavailability studies[9]	Phase 3 REJOICE study[10]
Doses	10 µg, 25 µg	4 µg, 10 µg, 25 µg
Time	Day 1 • 1, 0.5 h, and immediately before dosing • 1, 2, 4, 6, 8, 10, 12, 14, 18, and 24 h after dosing	Screening, days 1, 14, and 84 • Prior to dose on days 1 and 14 • 2, 4, 6, 10, and 24 h on days 1 and 14 • Once on day 84
Instrumentation	Liquid chromatography-tandem mass spectrometry	Gas chromatography-tandem mass spectrometry

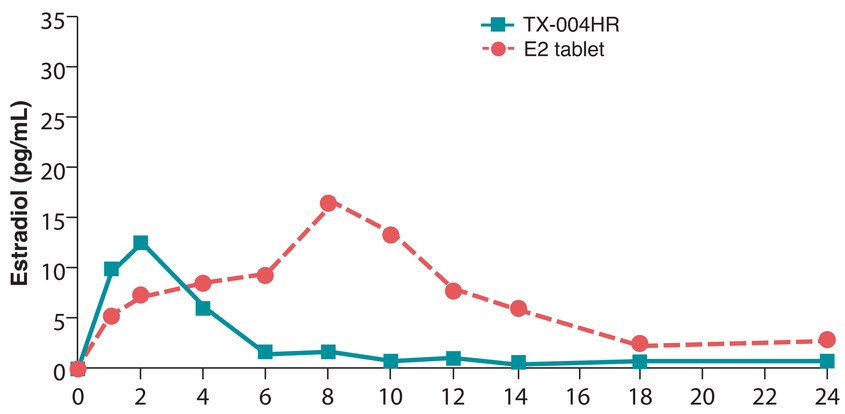
Results

***Bioavailability Studies*[9]**

- TX-004HR 10 µg and 25 µg resulted in statistically significantly lower E2 absorption PK parameters than with a vaginal E2 tablet at identical doses (**Figure 1**)
- TX-004HR had an AUC less than 1/3 that of the vaginal E2 tablet (**Table 2**)

Figure 1. Baseline-adjusted mean plasma concentration versus time for E2 with TX-004HR and vaginal E2 tablet[9]

A. 10-µg doses



B. 25-µg doses

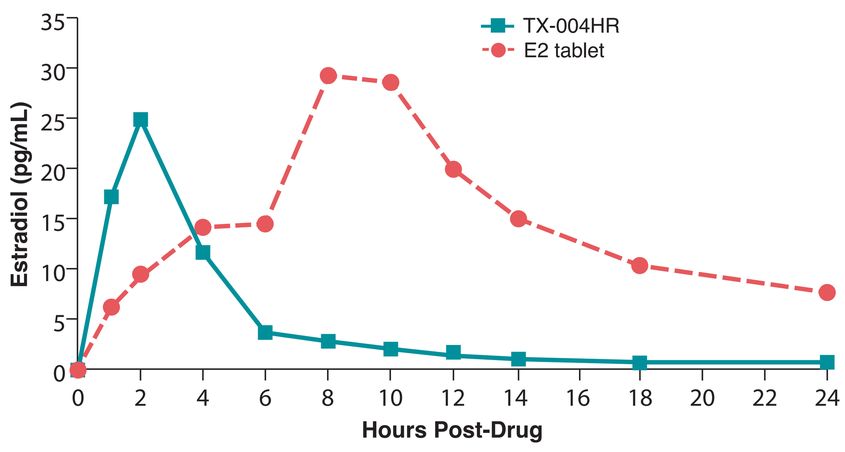


Table 2. Baseline adjusted PK parameters for E2 with TX-004HR and vaginal E2 tablet[9]

Baseline-Adjusted Mean*	TX-004HR 10 µg	Vagifem 10 µg	TX-004HR 25 µg	Vagifem 25 µg
AUC_{0-24}, pg*h/mL	49.62	132.92[a]	89.21	292.06[a]
C_{max}, pg/mL	14.38	20.38[b]	23.08	42.70[a]

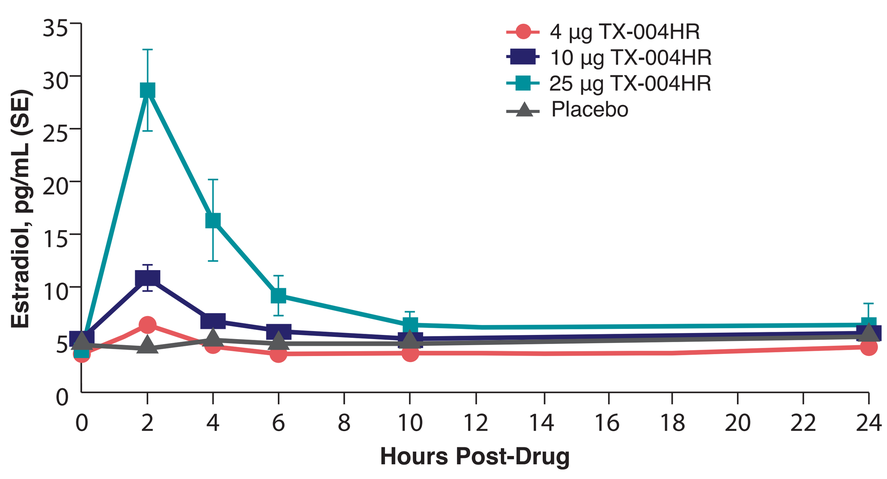
[a]P<0.0001; [b]P=0.0194 vs TX-004HR.

***Phase 3 REJOICE Trial*[10]**

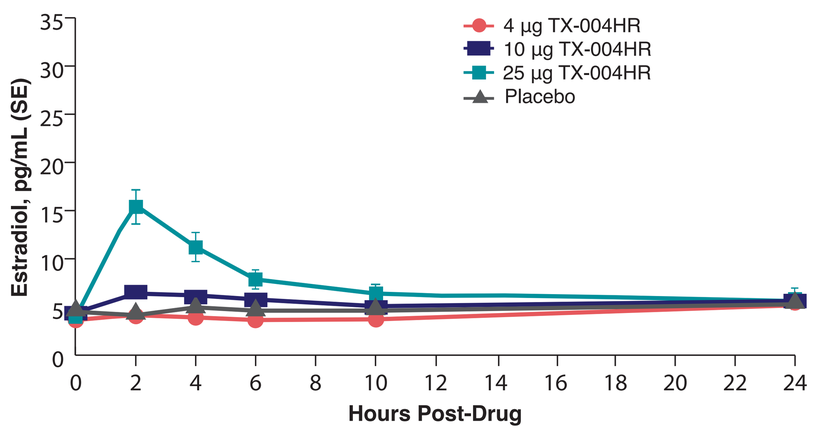
- E2 PK parameters for TX-004HR compared with placebo are shown in **Figure 2** and **Table 3**
  - TX-004HR 4 µg had no significant differences from placebo in E2 PK parameters
  - TX-004HR 10 µg was not different than placebo, with the exception of the C_{max} that was higher than placebo on day 1
  - TX-004HR 25 µg was associated with higher C_{avg} and AUC_{0-24} versus placebo on days 1 and 14
  - E2 concentrations on day 84 were similar to baseline and placebo for the three doses
- Estrone and estrone conjugate PK parameters with TX-004HR were similar to placebo across all doses (data not shown)
- TX-004HR may have up to 75-fold lower systemic E2 absorption than lower-dose oral E2 products in separate studies of postmenopausal women **(Table 3)**

Figure 2. Unadjusted mean serum E2 concentration with TX-004HR over time

A. Day 1



B. Day 14



C. Day 84

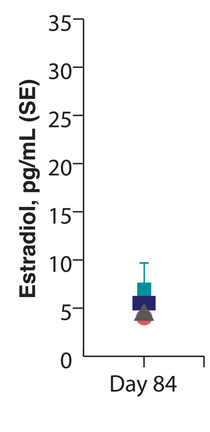


Table 3. Unadjusted PK parameters for E2 with TX-004HR in the REJOICE study[10] vs lower-dose oral E2 products in separate studies of postmenopausal women

Products	Sampling Day	AUC pg*h/mL	C_{max}, pg/mL	C_{avg}, pg/mL
TX-004HR 4 µg[10]	1 14	91.7 87.2	6.5 4.8	3.9 3.6
TX-004HR 10 µg[10]	1 14	138.2 110.1	10.9[a] 7.3	5.8 4.6
TX-004HR 25 µg[10]	1 14	217.4[b] 171.6[a]	29.8[c] 15.7[c]	9.1[b] 7.1[a]
Placebo[10]	1 14	116.6 104.2	6.6 5.5	4.9 4.3
Oral Activella®[11] 0.5 mg E2/0.1 mg NETA	1	697.3	26.5	—
Oral Angeliq®[12] 0.5 mg E2/0.25 mg DRSP	1	515.4	29.7	—

[a]P<0.05; [b]P<0.01; [c]P<0.0001 vs placebo; E2: 17β-estradiol; DRSP: drospirenone; NETA: norethindrone acetate.

Conclusions

- TX-004HR had negligible to very low systemic absorption of E2[9,10] with statistically significant improvements in VVA-associated, moderate to severe dyspareunia and vaginal dryness in a phase 3 study.[8]
- In phase 1 studies, TX-004HR had lower systemic E2 absorption versus a commercially available vaginal E2 tablet (Vagifem).[9]
- While not directly compared with oral E2 products in head-to-head studies,[11,12] the PK profile of TX-004HR exhibited very low systemic E2 absorption consistent with vaginal administration.
- While TX-004HR has not been studied in women with a history of breast cancer, its PK profile, especially with the lowest 4 µg dose, suggests that further study in this patient population should be considered.
- **Note: TX-004HR (TherapeuticsMD, Boca Raton, FL) has not been studied in women with known, suspected, or a history of breast cancer. These women were excluded from these studies. Use in patients with known, suspected, or history of breast cancer is contraindicated in the current FDA-approved labeling for this class of products.**

References

1. Mac Bride MB, et al. *Mayo Clin Proc* 2010;85:87-94. **2.** Crandall C, et al. *Menopause* 2004;11:519-530. **3.** NAMS. *Menopause* 2013;20:888-902. **4.** Kadakia KC, et al. *Oncologist* 2016;21:539-546. **5.** ACOG. *Obstet Gynecol* 2016;127:e93-96. **6**. NAMS. *Menopause*. 2013;20:888-902. **7**. de Villiers TJ, et al. *Climacteric*. 2016;19:313-315. **8.** Constantine G, et al. *Menopause* 2017;24:409-416. **9.** Pickar JH, et al. *Climacteric* 2016;19:181-187. **10.** Archer DF, et al. *Menopause* 2016 2017;24:510-516. **11.** Activella Physician Insert. Dec 2006. **12.** Angeliq Prescribing Information. Feb 2012.

Disclosures

- Dr. Goldfarb has received consultant fees from Sermonix and Intrarosa; and research support from Paxman and Valeant. Dr. Parish is a member of the advisory board for AMAG, Allergen, and Duchesnay; is a consultant for Strategic Scientific Technologies (SST); and has served on the speaker's bureau for AMAG and Valeant. Drs. Bernick and Mirkin are employees of TherapeuticsMD with stock/stock options. Dr. Bernick is also a Board member of TherapeuticsMD.
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