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

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Background

- Approximately 30M US postmenopausal women with symptomatic vulvar and vaginal atrophy (VVA) remain untreated,[1] 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[2,3]
- TX-004HR is an applicator-free, softgel vaginal insert containing ultra-low doses of estradiol (E2; 4 or 10 µg), specifically designed to minimize systemic absorption of E2 while treating symptomatic VVA[4]
- 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
  - Earliest improvements were observed for (**Table 1**)
    - Moderate to severe dyspareunia at 2 weeks with all TX-004HR doses
    - Vaginal dryness at 2 weeks with TX-004HR 10 µg and 6 weeks with 4 µg
  - No unexpected safety findings were observed through 12 weeks; no long-term safety data were collected

Table 1. Earliest statistically significant improvements with TX-004HR compared with placebo[4]

Endpoints	TX-004HR 4 µg		TX-004HR 10 µg	
	Week	*P*-value	Week	*P*-value
Percentage of superficial cells[a]	2	<0.0001	2	<0.0001
Percentage of parabasal cells[a]	2	<0.0001	2	<0.0001
Vaginal pH[a]	2	<0.0001	2	<0.0001
Dyspareunia[a]	2	0.026	2	0.0019
Vaginal dryness[b]	6	0.0094	2	0.0019

P-value vs placebo. [a]Four co-primary endpoints (measured at 12 weeks); [b]Secondary endpoint.

Objective

- Determine the pharmacokinetic (PK) profile of TX-004HR (4 and 10 µg) in a subset of subjects enrolled in the phase 3 REJOICE trial

Methods

Phase 3 REJOICE Trial[4]

- PK profiles of TX-004HR 4 µg and 10 µg were evaluated in a subset of subjects (n=54) who participated in the REJOICE trial, a phase 3, double-blind, placebo-controlled trial
- Participants were menopausal 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 2**

Table 2. PK Methodology for the REJOICE trial

Estradiol Assessment	Phase 3 REJOICE study[5]
Doses	4 µg, 10 µg
Time of blood sampling	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	Gas chromatography-tandem mass spectrometry

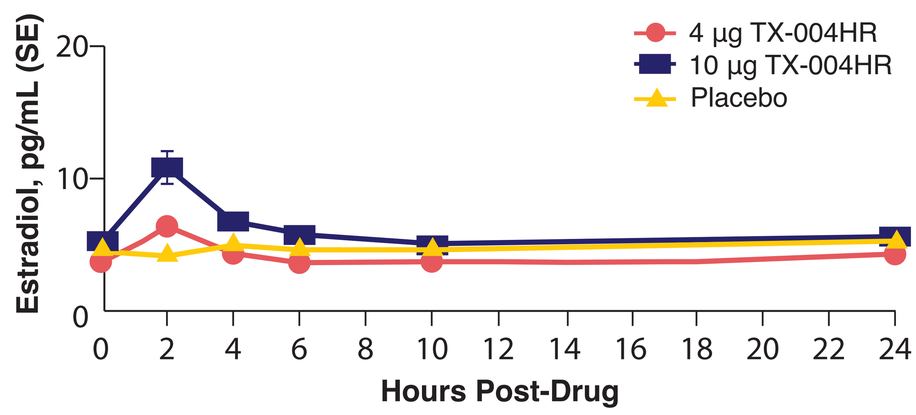
Results

Phase 3 REJOICE Trial[5]

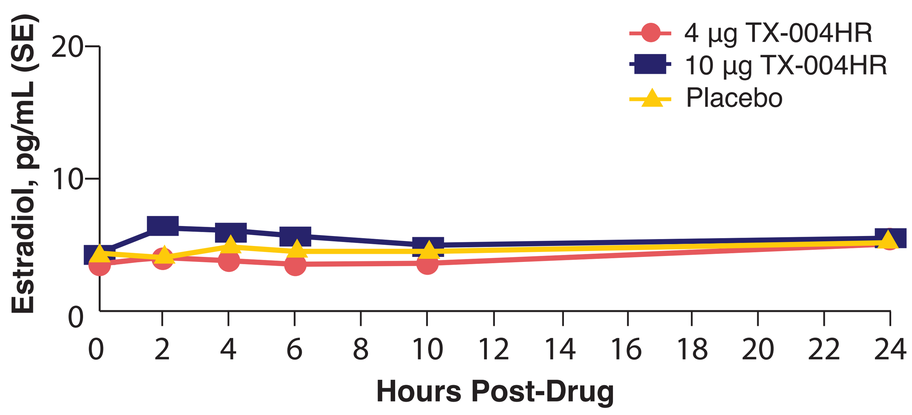
- E2 PK parameters for TX-004HR compared with placebo are shown in **Figure 1** and **Table 3**
  - TX-004HR 4 µg had no significant differences from placebo in E2 PK parameters
  - TX-004HR 10 µg was not different than placebo, with the exception of the C_{max} that was higher than placebo on day 1
  - Day 14 mean serum levels were lower than those on day 1
  - Consistent 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
  - E2 concentrations on day 84 were similar to baseline and placebo for the two doses

Figure 1. Unadjusted mean serum estradiol concentration with TX-004HR over time

A. Day 1



B. Day 14



C. Day 84

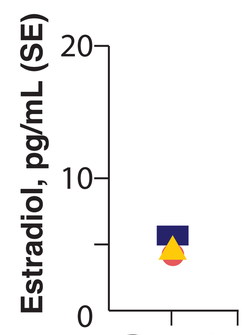


Table 3. Unadjusted PK parameters for estradiol with TX-004HR in the REJOICE study[5]

Day	Unadjusted Mean	TX-004HR 4 µg (n=18)	TX-004HR 10 µg (n=19)	Placebo (n=17)
Day 1	AUC, pg*h/mL	91.7	138.2	116.6
	C_{max}, pg/mL	6.5	10.9[a]	6.6
	C_{avg}, pg/mL	3.9	5.8	4.9
Day 14	AUC, pg*h/mL	87.2	110.1	104.2
	C_{max}, pg/mL	4.8	7.3	5.5
	C_{avg}, pg/mL	3.6	4.6	4.3

[a]*P*<0.05; vs placebo.

Conclusions

- TX-004HR, a soluble E2, softgel vaginal insert, given in a twice-weekly regimen (following daily doses for 14 days), resulted in negligible to very low systemic absorption of estradiol[5] with statistically significant improvements in VVA-associated, moderate to severe dyspareunia and vaginal dryness[4]
  - Serum E2 levels were maintained within the normal postmenopausal range (9.3 ng/mL)[6]
- Lower serum E2 levels on day 14 vs day 1 suggest vaginal wall regeneration and/or improvement in vaginal cell metabolic activity
- The ability of TX-004HR to reduce the symptoms of VVA while maintaining E2 concentrations within the range of postmenopausal levels throughout the dosing period is relevant given the progressive nature of VVA, which may require chronic treatment

References

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Disclosures

- Dr. Constantine consults to pharmaceutical companies including but not limited to TherapeuticsMD and has stock options with TherapeuticsMD. Drs. Shadiack and Mirkin are employees of TherapeuticsMD with stock/stock options. Dr. Inskeep consults with pharmaceutical companies including but not limited to TherapeuticsMD. Dr. Pickar is a consultant for Pfizer, Shionogi Inc, and TherapeuticsMD and has stock options with TherapeuticsMD. Dr. Bernick is an employee of TherapeuticsMD with stock/stock options; and is also a Board member.
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