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

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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 (ultra-low doses of solubilized 17β-estradiol [E2; 4, 10 or 25 µg], softgel vaginal insert) was designed to rapidly treat VVA symptoms without increasing systemic E2, to be easily inserted without an applicator, and to completely dissolve to minimize discharge.[4]

Objective

- To review TX-004HR phase 3 data showing improvements in menopausal VVA symptoms and phase 1 and 3 evidence of negligible to very low systemic E2 absorption

Methods

***REJOICE Trial*[4]**

- The REJOICE trial was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study of TX-004HR 4 µg, 10 µg, and 25 µg compared with placebo
- Participants were menopausal women (aged 40 to 75 years; BMI ≤38 kg/m^2) with symptomatic VVA and a most bothersome symptom of moderate to severe dyspareunia
- Treatments were self-administered once daily for 2 weeks, then twice weekly for 10 weeks
- Four co-primary efficacy endpoints were change from baseline to week 12 in percentages of superficial and parabasal cells, vaginal pH, and severity of dyspareunia and secondary endpoints included severity of vaginal dryness
- Safety endpoints included endometrial histology and adverse events (AEs)
- Pharmacokinetic (PK) parameters (PK substudy, **Table 1**) were assessed in a subset of participants[5]

***Bioavailability Studies*[6]**

- 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 estradiol tablet 10 µg and 25 µg (Vagifem®, Novo Nordisk, Plainsboro, NJ), respectively
- Participants were healthy menopausal women (aged 40-65 years; BMI 18.5 to 30.0 kg/m^2)
- Women sequentially received a single dose of TX-004HR or a vaginal estradiol tablet depending on randomization
- Details on sampling time and assessments are found in **Table 1**

Table 1. PK Methodology for the REJOICE and bioavailability studies

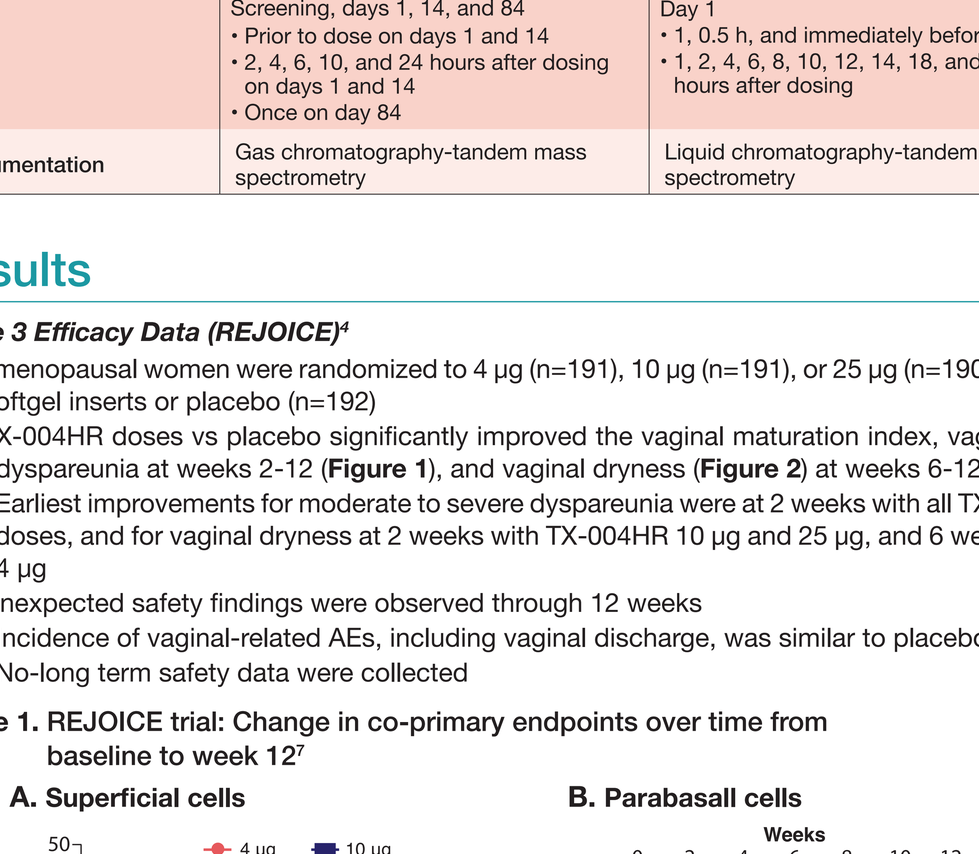
E2 Assessment	Phase 3 REJOICE study[5]	Phase 1 studies[6]
Doses	4 µg, 10 µg, 25 µg	10 µg, 25 µg
Time	Screening, days 1, 14, and 84 • Prior to dose on days 1 and 14 • 2, 4, 6, 10, and 24 hours after dosing on days 1 and 14 • Once on day 84	Day 1 • 1, 0.5 h, and immediately before dosing • 1, 2, 4, 6, 8, 10, 12, 14, 18, and 24 hours after dosing
Instrumentation	Gas chromatography-tandem mass spectrometry	Liquid chromatography-tandem mass spectrometry

Results

***Phase 3 Efficacy Data (REJOICE)*[4]**

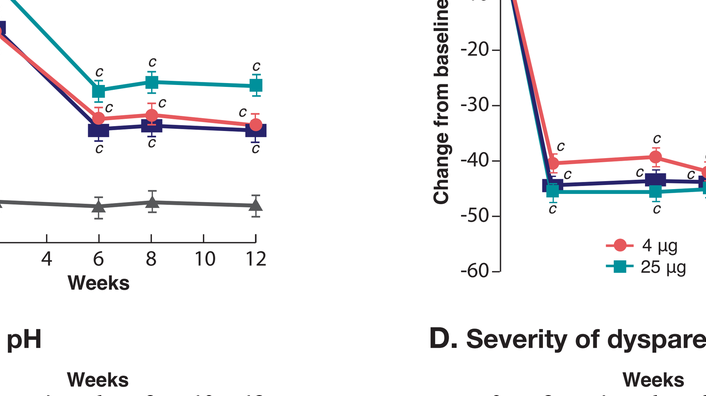
- 764 menopausal women were randomized to 4 µg (n=191), 10 µg (n=191), or 25 µg (n=190) vaginal E2 softgel inserts or placebo (n=192)
- All TX-004HR doses vs placebo significantly improved the vaginal maturation index, vaginal pH, and dyspareunia at weeks 2-12 (**Figure 1**), and vaginal dryness (**Figure 2**) at weeks 6-12
  - Earliest improvements for moderate to severe dyspareunia were at 2 weeks with all TX-004HR doses, and for vaginal dryness at 2 weeks with TX-004HR 10 µg and 25 µg, and 6 weeks with 4 µg
- No unexpected safety findings were observed through 12 weeks
  - Incidence of vaginal-related AEs, including vaginal discharge, was similar to placebo
  - No-long term safety data were collected

Figure 1. REJOICE trial: Change in co-primary endpoints over time from baseline to week 12[7]



[a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001 for TX-004HR vs placebo.

Figure 2. REJOICE trial: Change in dryness (secondary endpoint) over time from baseline to week 12



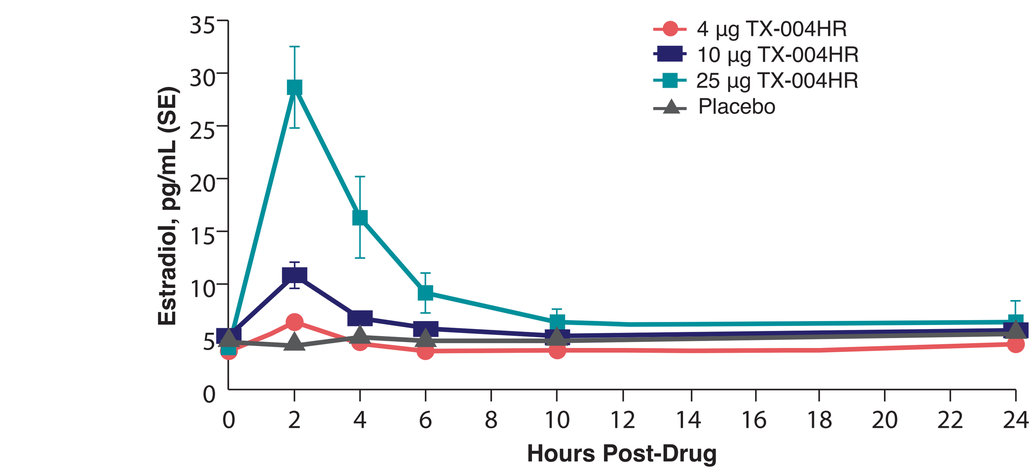
[a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001, [d]*P*<0.0001 for TX-004HR vs placebo.

Phase 1 and 3 PK Data

***REJOICE Trial*[5]**

- Systemic E2 levels (n=72) for 4 µg and 10 µg TX-004HR were similar to placebo on days 1 and 14, and at day 84 (**Figure 3)**
- See poster by Goldfarb et al for all PK parameters (TX-004HR PK)
  - TX-004HR 4 µg had no significant differences from placebo in E2 PK parameters
  - PK with TX-004HR 10 µg was not different than with 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 $AUC_{0\text{-}24}$ versus placebo on days 1 and 14
  - E2 concentrations on day 84 were similar to baseline and placebo for the three doses

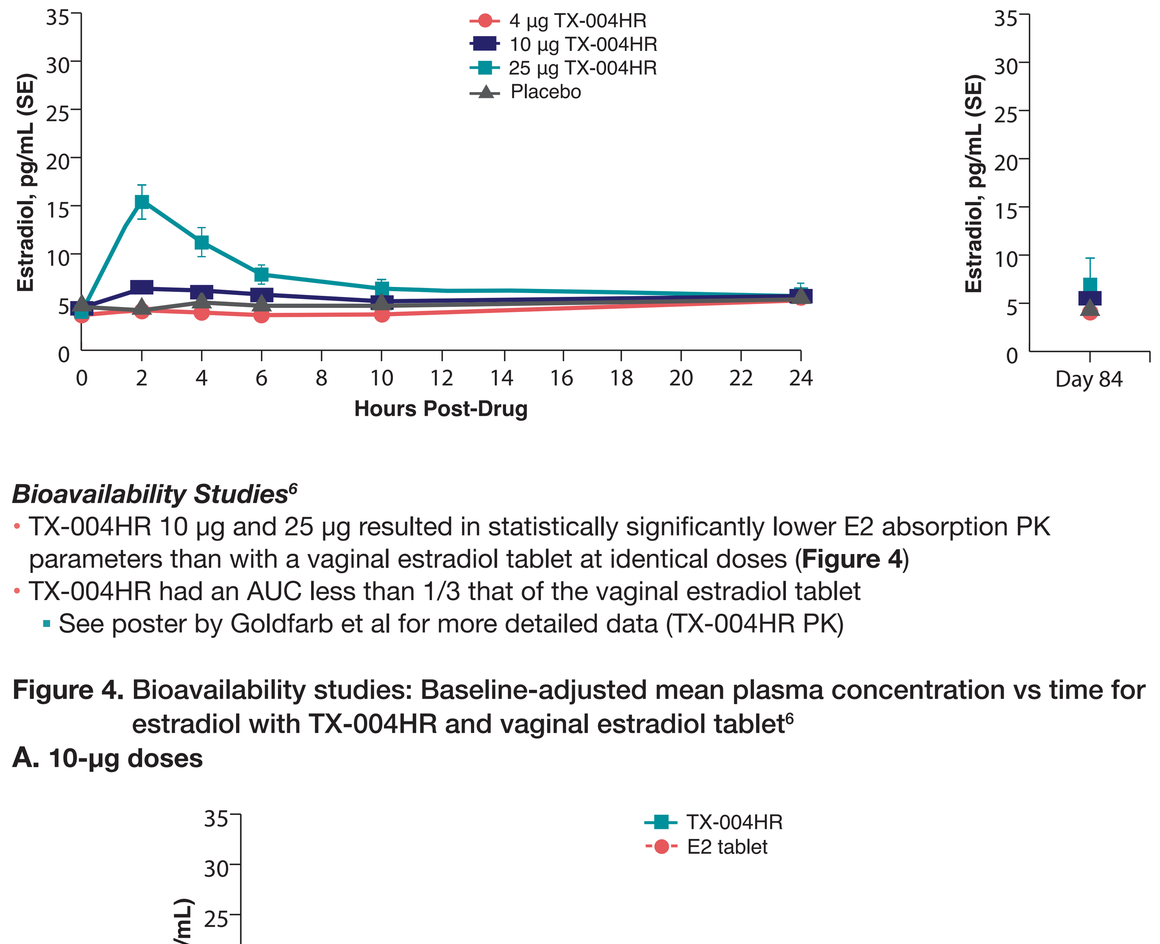
Figure 3. REJOICE trial: Unadjusted mean serum estradiol concentration with TX-004HR on days 1, 14 and 84



***Bioavailability Studies*[6]**

- TX-004HR 10 µg and 25 µg resulted in statistically significantly lower E2 absorption PK parameters than with a vaginal estradiol tablet at identical doses (**Figure 4**)
- TX-004HR had an AUC less than 1/3 that of the vaginal estradiol tablet
  - See poster by Goldfarb et al for more detailed data (TX-004HR PK)

Figure 4. Bioavailability studies: Baseline-adjusted mean plasma concentration vs time for estradiol with TX-004HR and vaginal estradiol tablet[6]



Conclusions

- In the phase 3 REJOICE trial, TX-004HR improved signs and symptoms of VVA as early as 2 weeks with TX-004HR 4 µg, 10 µg, and 25 µg with negligible to very low systemic E2 absorption.
- TX-004HR also provided lower systemic E2 levels than equivalent doses of an approved vaginal E2 tablet in phase 1 studies.

References

1. Wysocki S, et al. *Clin Med Insights Reprod Health.* 2014;8:23-30. **2.** ACOG Committee on Gyncologic Practice. *Obstet Gynecol.* 2016; 127:e93-96. **3.** NAMS. *Menopause*. 2013;20:888-902. **4.** Constantine G, et al. *Menopause*. 2017;24:409-416. **5.** Archer DF, et al. *Menopause*. 2017;24:510-516. **6.** Pickar JH, et al. *Climacteric*. 2016;19:181-187. **7.** Simon JA, et al. *Maturitas*. 2017;99:51-58.

Disclosures

- Dr. Parish is a member of advisory boards 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. Dr. Larkin is a member of advisory boards for AMAG, Palatin Technologies, and Valeant. Dr. Simon has served (within the past year, or current) as a consultant/advisor to AbbVie, Allergan Plc, AMAG, Ascend Therapeutics, Azure Biotech, Millendo Therapeutics, Nuelle, Radius Health, Regeneron, Roivant Sciences, Sanofi SA, Sebela, Sermonix, Shionogi, Symbiotec Pharmalab, TherapeuticsMD, and Valeant; has received (within the past year, or current) grant/research support from AbbVie, Allergan Plc, Agile Therapeutics, Bayer Healthcare, New England Research Institute, ObsEva SA, Palatin Technologies, Symbio Research, and TherapeuticsMD; has also served (within the past year, or current) on the speaker's bureaus of Novo Nordisk, Shionogi, and Valeant. Dr. Bernick is an employee of TherapeuticsMD with stock/stock options, and is also a Board member. Dr. Mirkin is an employee of TherapeuticsMD with stock/stock options.
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