

# A vaginal estradiol softgel capsule, TX-004HR, has negligible to very low systemic absorption of estradiol: Efficacy and pharmacokinetic data review



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## ABSTRACT

This paper reviews the efficacy, safety, and systemic absorption of estradiol with TX-004HR, an investigational, low-dose 17 $\beta$ -estradiol vaginal softgel capsule, designed to treat vulvar and vaginal atrophy (VVA) in postmenopausal women, with an improved user experience. In phase 2 (NCT02449902) and phase 3 REJOICE (NCT02253173) studies, TX-004HR significantly improved the proportions of vaginal superficial and parabasal cells and vaginal pH, and in the phase 3 study decreased the severity of dyspareunia, vaginal dryness, and vulvar and/or vaginal itching or irritation. In two randomized, phase 1 trials, estradiol  $C_{max}$  and  $AUC_{0-24}$  were significantly lower with 10  $\mu$ g and 25  $\mu$ g TX-004HR than with the same doses of an approved vaginal estradiol tablet. A substudy ( $n = 72$ ) of the REJOICE trial showed that estradiol  $C_{avg}$  and  $AUC_{0-24}$  with 4  $\mu$ g and 10  $\mu$ g TX-004HR were not different from placebo on days 1 and 14. While TX-004HR 25  $\mu$ g was associated with higher  $C_{avg}$  and  $AUC_{0-24}$  versus placebo on days 1 and 14, these levels remained within the postmenopausal range. Estradiol day-84 values for all three doses were not different from placebo, demonstrating no estradiol accumulation. All TX-004HR doses were well tolerated and had an acceptable safety profile in all reviewed studies. The local vaginal efficacy of TX-004HR was significantly better than that of placebo, while the overall safety profile was similar to that of placebo. Negligible to very low systemic estradiol absorption was observed whether given at 4, 10, or 25  $\mu$ g. If approved, TX-004HR may be an alternative option for women with symptomatic VVA without increasing mean systemic estradiol absorption above postmenopausal levels.

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## 1. Introduction

Vulvar and vaginal atrophy (VVA), with characteristic symptoms of dyspareunia, vaginal dryness, and vulvar and vaginal irritation and itching (components of the more encompassing term genitourinary syndrome of menopause [GSM] [1]), is experienced by up to 50% of postmenopausal women, due to the decline in circulating estrogens [2–5]. These symptoms persist and are progressive without treatment, and can negatively impact quality of life [2,3,6,7]. Although treatment options are available, surveys show that postmenopausal women are dissatisfied with current VVA products, citing concerns about safety, efficacy, administration methods, and messiness [2,5,8]. Other survey results show that only 7% of women use prescription only VVA therapy [5], even though 32 million postmenopausal women in the US are estimated to have symptomatic VVA [5,9]. Thus, newer options with better efficacy, safety, and convenience are needed.

TX-004HR (TherapeuticsMD, Inc., Boca Raton, FL) is a new, investigational, low-dose solubilized 17 $\beta$ -estradiol, muco-adhesive, vaginal softgel capsule for treating VVA in postmenopausal women [10]. It was designed to locally treat vaginal tissue with rapid onset and negligible to very low systemic estradiol exposure [10], and allows for easy insertion without an applicator, use at any time of the day, and less mess and discharge than creams and tablets.

This article reviews efficacy, safety, and/or estradiol pharmacokinetic (PK) data following TX-004HR treatment in postmenopausal women with VVA from two phase 1 PK studies (10  $\mu$ g and 25  $\mu$ g) [11], a phase 2 efficacy study (10  $\mu$ g; NCT02449902) [12], and the phase 3 REJOICE trial (4  $\mu$ g, 10  $\mu$ g, and 25  $\mu$ g; NCT02253173) [10,13].

## 2. TX-004HR efficacy data

### 2.1. Efficacy: phase 2 study

#### 2.1.1. Study design and participants

This single-center, double-blind, placebo-controlled, phase 2 trial randomized healthy postmenopausal women to 10  $\mu$ g TX-004HR or placebo daily for 14 days (Table 1) [12]. Changes from baseline after 14 days of treatment in the percentages of vaginal parabasal, superficial, and intermediate cells; vaginal pH; and severity of most bothersome VVA symptom (MBS) were the study's main efficacy endpoints. Vaginal mucosa and adverse events (AEs) were also assessed.

Participants (40–75 years; body mass index [BMI]  $\leq$ 34.0 kg/m<sup>2</sup>) had  $\leq$ 5% vaginal superficial cells, vaginal pH  $>$ 5.0, estradiol level  $\leq$ 50 pg/mL; and moderate-to-severe vaginal dryness, dyspareunia,

vaginal and/or vulvar irritation/itching, dysuria, or vaginal bleeding with sexual activity [12]. Women with contraindications to estrogens were excluded. Any hormonal products could not be taken within their specified washout time, and any drugs that could interfere with estrogens within 28 days.

A total of 50 women were randomized to TX-004HR (n=24) or placebo (n=26); two women taking placebo discontinued the study (Fig. 1). Mean age was approximately 62 years and mean BMI approximately 26.9 kg/m<sup>2</sup> [12].

#### 2.1.2. Vaginal physiology improved with TX-004HR 10 $\mu$ g versus placebo

Percentages of superficial cells (35.2 percentage point changes with TX-004HR vs 8.8 with placebo;  $P < 0.001$ ) and intermediate cells (18.7 vs  $-3.5$ ;  $P = 0.002$ ) significantly increased, and the percentage of parabasal cells ( $-54.4$  vs  $-4.8$ ;  $P < 0.001$ ) and vaginal pH ( $-0.97$  vs  $-0.34$ ;  $P < 0.001$ ) significantly decreased after 2 weeks of treatment [12]. Severity of the MBS was not significantly different between groups; however, the severity of individual symptoms of dryness and dyspareunia decreased by approximately 1.0 and 0.8 points, respectively, with TX-004HR versus approximately 0.7 and 0.5 points with placebo. Lastly, TX-004HR improved vaginal epithelial integrity and vaginal secretions significantly more than placebo.

Treatment-emergent adverse events (TEAEs) were reported by a total of 14 (28%) women (11 taking TX-004HR and 3 taking placebo); the most common TEAEs from the TX-004HR group included vaginal dysplasia (n=3) and hot flush (n=2), and from the placebo group, vaginal hemorrhage (n=2) [14]. Most TEAEs were mild to moderate and no serious AEs were reported [12].

### 2.2. Efficacy and safety in the phase 3 REJOICE trial

#### 2.2.1. Study design and outcomes

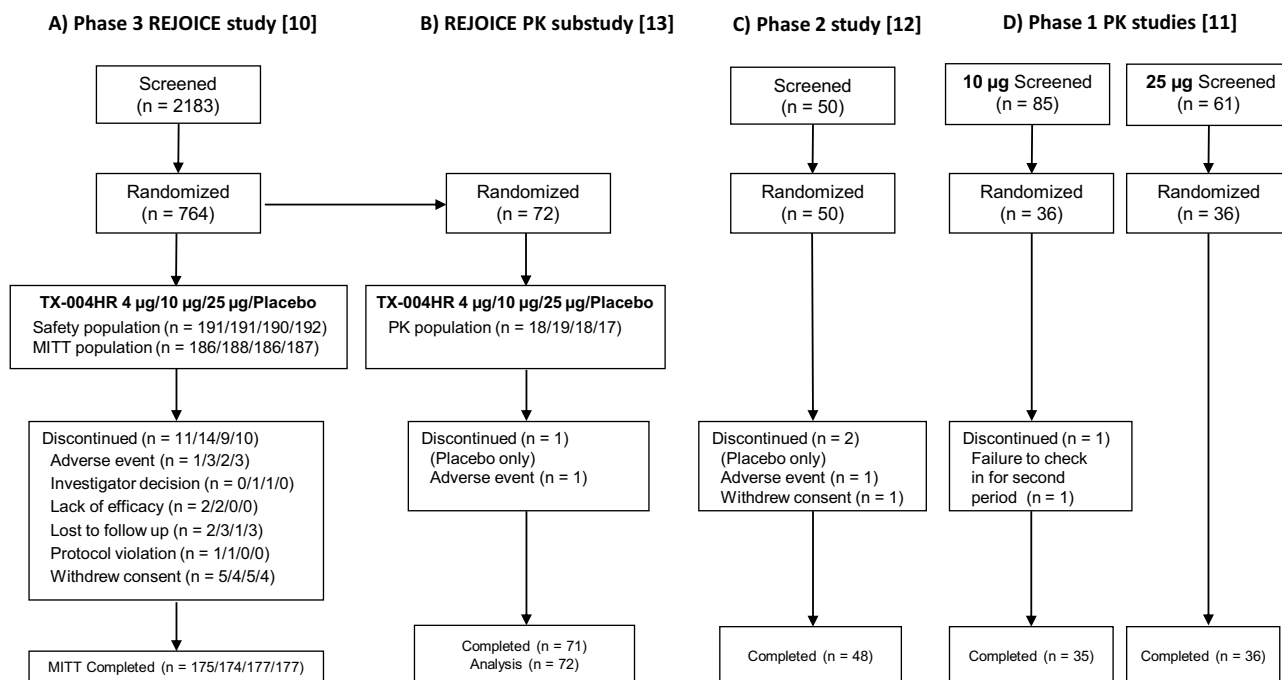
The REJOICE trial was a multicenter, randomized 1:1:1:1, double-blind, 12-week, phase 3 trial that evaluated the efficacy and safety of TX-004HR (4  $\mu$ g, 10  $\mu$ g, or 25  $\mu$ g) compared with placebo in postmenopausal women with moderate to severe dyspareunia due to VVA (Table 1) [10]. Vaginal capsules were self-administered once daily for 2 weeks and then twice weekly for 10 weeks. Capsules could be inserted at any time of the day, but around the same time (within the hour) on subsequent days.

A total of 89 study sites in the US and Canada contributed data on 4 co-primary endpoints: changes from baseline in percentages of vaginal superficial and parabasal cells, vaginal pH, and severity of dyspareunia at week 12 versus placebo [10]. Other VVA symptoms and AEs were evaluated.

**Table 1**  
Study design of the four reviewed studies of the TX-004HR vaginal estradiol softgel capsule.

Study	Design (n)	Treatments	Duration	Inclusion criteria	Study endpoints
Constantine et al., 2016 [10] REJOICE	Phase 3, placebo-controlled, randomized, double-blind (n = 764) NCT02253173	TX-004HR (4, 10, or 25 µg) or matching placebo	12 weeks	Postmenopausal women (40–75 years) with ≤5% superficial cells, vaginal pH >5.0, MBS of moderate-to-severe vaginal pain associated with dyspareunia, onset of dyspareunia after menopause, BMI ≤38 kg/m <sup>2</sup> , and anticipating sexual activity during study	Primary (efficacy) <ul style="list-style-type: none"> <li>Change in percentage of vaginal superficial and parabasal cells, vaginal pH, and severity of dyspareunia associated with VVA from baseline to week 12 compared with placebo</li> <li>Key secondary (efficacy) <ul style="list-style-type: none"> <li>Change from baseline to weeks 2, 6, and 8 compared with placebo in percentage of vaginal superficial and parabasal cells, vaginal pH, and severity of dyspareunia</li> <li>Change from baseline to weeks 2, 6, 8, and 12 in the severity of vaginal dryness and vulvar and/or vaginal itching or irritation associated with VVA vs placebo</li> <li>Change in visual exam of the vaginal mucosa from baseline to weeks 2–12 vs placebo</li> </ul> </li> </ul>
Archer et al., 2016 [13] REJOICE PK substudy	Phase 3, placebo-controlled, randomized, double-blind (n = 72)	TX-004HR (4, 10, or 25 µg) or matching placebo	84 days	Postmenopausal women (40–75 years) with ≤5% superficial cells, vaginal pH >5.0, MBS of moderate-to-severe vaginal pain associated with dyspareunia, onset of dyspareunia after menopause, BMI ≤38 kg/m <sup>2</sup> , and anticipating sexual activity during study	PK endpoints <ul style="list-style-type: none"> <li>Area under the serum concentration-time curve, average concentration, peak concentration from 0 to 24 h, and time to maximum concentration for estradiol, estrone, and estrone conjugates on days 1 and 14</li> <li>Mean serum estradiol concentrations on day 84 (trough value of estradiol)</li> </ul>
Pickar et al., 2016 [12]	Phase 2 pilot, placebo-controlled, randomized, double-blind, single center (n = 50) NCT02449902	TX-004HR (10 µg) or placebo	14 days	Postmenopausal women (40–75 years) with BMI ≤34 kg/m <sup>2</sup> , ≤5% superficial cells, vaginal pH >5.0, E <sub>2</sub> level ≤50 pg/mL, and at least 1 moderate-to-severe VVA symptom (dryness, pain associated with sexual activity, vaginal and/or vulvar irritation/itching, dysuria, or vaginal bleeding associated with sexual activity)	Efficacy endpoints <ul style="list-style-type: none"> <li>Change from baseline to day 15 in percentage of vaginal parabasal, superficial, and intermediate cells; vaginal pH; and severity of MBS</li> <li>Key secondary (efficacy) <ul style="list-style-type: none"> <li>Change from baseline to day 15 in investigator assessment of vaginal mucosa (secretions, epithelial integrity, epithelial surface thickness, and color)</li> </ul> </li> </ul>
Pickar et al., 2016 [11]	Randomized, two-period, single-dose, open-label, two-way cross-over, relative bioavailability (2 studies: 10 µg, n = 35; 25 µg n = 36)	TX-004HR (10 and 25 µg) and estradiol vaginal tablet (Vagifem®)	24 h for dosing and 14-day washout between dosing periods	Healthy, postmenopausal women (40–65 years) with BMI between 18.50 and 29.99 kg/m <sup>2</sup>	Primary (PK) <ul style="list-style-type: none"> <li>Area under the concentration-time curve from 0 to 24 h and maximum concentration for estradiol, estrone, and estrone sulfate (baseline adjusted and unadjusted)</li> </ul> Secondary (PK) <ul style="list-style-type: none"> <li>Time to maximum concentration</li> </ul>

MBS, most bothersome symptom; PK, pharmacokinetics; VVA, vulvovaginal atrophy.



**Fig. 1.** Flow of participants throughout the reviewed clinical studies: A) Phase 3 REJOICE study, B) REJOICE PK substudy, C) Phase 2 efficacy study, and D) Phase 1 PK studies.

### 2.2.2. Study participants

Eligible participants were healthy postmenopausal women aged 40–75 years, with a BMI  $\leq 38$  kg/m<sup>2</sup>, and were likely to have vaginal sexual intercourse during the study [10]. Women had  $\leq 5\%$  superficial vaginal cells, vaginal pH  $> 5.0$ , and moderate to severe dyspareunia self-identified as their MBS of VVA. Key exclusion criteria were endometrial hyperplasia, undiagnosed vaginal bleeding, and others typical of hormone therapy studies. Women could not have taken any hormone products (by any route) containing estrogens, progestins, androgens, or selective estrogen receptor modulators within specified washout periods.

The REJOICE study randomized 764 women to TX-004HR 4 µg (n = 191), 10 µg (n = 191), 25 µg (n = 190), or placebo (n = 192; Fig. 1) [10]. The majority (94%) of the modified intent-to-treat population completed the study. Participants had a mean age of 59 years, mean BMI of 27 kg/m<sup>2</sup>, and were mostly white (~87%).

### 2.2.3. TX-004HR improved vaginal physiology and symptom severity

TX-004HR (4 µg, 10 µg, or 25 µg) significantly altered percentages of vaginal superficial and parabasal cells, vaginal pH, and severity of dyspareunia as early as 2 weeks ( $P < 0.001$  for all, except dyspareunia  $P < 0.05$ ). These significant improvements were maintained over the 12-week study (Fig. 2A–D) [10]. Vaginal dryness severity significantly improved by week 2 with 10 µg and 25 µg TX-004HR ( $P < 0.01$  for both), and by week 6 with 4 µg ( $P < 0.01$ ), and remained improved with all TX-004HR doses for up to 12 weeks ( $P < 0.01$  for 4 µg and  $P < 0.001$  for 10 µg and 25 µg). Significant decreases in severity of vulvar and/or vaginal itching or irritation were also noted with 10 µg ( $P = 0.0055$ ) and 25 µg TX-004HR ( $P = 0.0263$ ) relative to placebo at week 12 (4 µg was not significant versus placebo [ $P = 0.0503$ ]).

### 2.2.4. TX-004HR was well tolerated

All doses of TX-004HR were well tolerated and had an acceptable safety profile [10]. The treatment-emergent AE profile was not clinically significantly different between TX-004HR and placebo, and most AEs were mild to moderate in severity. Headache was

the most commonly reported TEAE, and was the only treatment-related AE numerically higher with TX-004HR (4 µg, 3.7%) versus placebo (3.1%), while vaginal discharge and vaginal pruritis were reported more with placebo. Eight women reported 9 serious AEs, which were not considered related to treatment.

## 3. TX-004HR pharmacokinetic studies

### 3.1. Estradiol absorption with TX-004HR versus a commercially available vaginal estradiol tablet: phase 1 trials

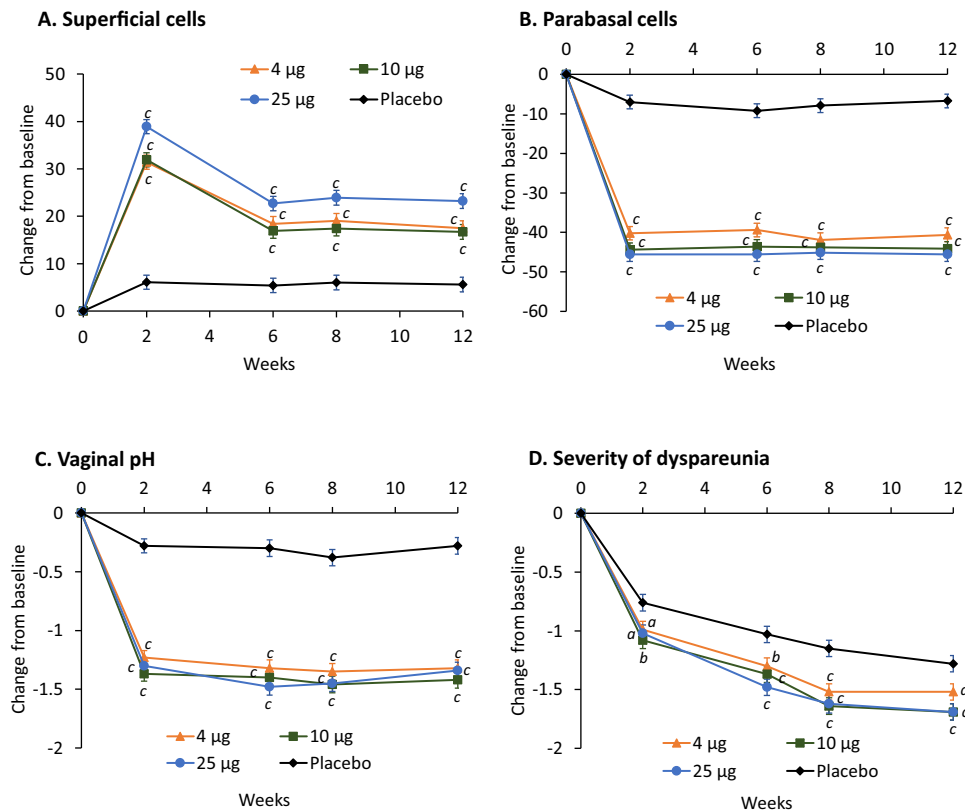
#### 3.1.1. Study design and outcomes

Both phase 1 PK studies were randomized, 2-way crossover, open-label trials, and evaluated the PK of single doses of TX-004HR (10 µg or 25 µg) versus the same doses of an FDA-approved solid vaginal estradiol tablet (Vagifem, Novo Nordisk, Plainsboro, NJ; Table 1) [11,15]. Women were randomly assigned to either treatment taken sequentially during 2 study periods separated by a 2-week washout. Treatments were administered by trained female study personnel, with TX-004HR capsules inserted 1–2 inches into the vagina. The comparator was inserted per the manufacturer's instructions with their supplied vaginal applicator. Women remained supine for 4 h after treatment, received standard scheduled meals, and avoided strenuous exercise.

Estradiol concentrations were assessed by liquid chromatography-tandem mass spectrometry in samples taken at several times before dosing and up to 24 h after dosing [11]. The lower limit of quantification (LLOQ) for estradiol was 1.0 pg/mL in the 10-µg study and 2.0 pg/mL in the 25-µg study. The primary PK endpoints included area under the concentration–time curve from 0 to 24 h ( $AUC_{0-24}$ ) and maximum concentration ( $C_{max}$ ) for estradiol (baseline adjusted and unadjusted); time to  $C_{max}$  ( $t_{max}$ ) was a secondary endpoint.

#### 3.1.2. Study participants

Participants in both phase 1 PK studies were postmenopausal women aged 40–65 years with a BMI between 18.5 and 30.0 kg/m<sup>2</sup> [11]. Women with contraindications to estrogens were excluded.



**Fig. 2.** REJOICE trial efficacy data: Change in co-primary endpoints over time from baseline to week 12: (A) superficial cells, (B) parabasal cells, (C) vaginal pH, and (D) severity of dyspareunia [10]. <sup>a</sup> $P < 0.05$ , <sup>b</sup> $P < 0.01$ , <sup>c</sup> $P < 0.001$  for TX-004HR versus placebo.

Participants could not have taken any products containing hormones within specified time required for washout; or prescription drug use within the last 2 weeks.

The study that evaluated 10 µg TX-004HR enrolled and randomized 36 women, and 35 women completed the study; 1 woman taking the comparator did not return during the second study period (Fig. 1) [11]. Study completers had a mean age of 50.4 years and mean BMI of 25.4 kg/m<sup>2</sup>. The study that examined 25 µg TX-004HR enrolled and randomized 36 women, all of whom completed the study; mean age was 49.9 years and mean BMI was 25.6 kg/m<sup>2</sup>.

### 3.1.3. Estradiol absorption of TX-004HR versus comparator

Estradiol concentrations were overall lower with TX-004HR 10 µg and 25 µg than with the vaginal estradiol tablet at their respective doses (Fig. 3) [11]. The  $C_{max}$  for estradiol was significantly lower with TX-004HR than with the comparator at both the 10-µg dose (14.4 versus 20.4 pg/mL, respectively;  $P = 0.019$ ) and the 25-µg dose (23.1 versus 42.7 pg/mL;  $P < 0.001$ ). Systemic exposure to estradiol, as measured by the  $AUC_{0-24}$ , was also significantly lower among women receiving TX-004HR versus the vaginal tablet at 10 µg (49.6 versus 132.9 pg·h/mL;  $P < 0.001$ ) and 25 µg (89.2 versus 292.1 pg·h/mL;  $P < 0.001$ ). In addition, peak estradiol concentrations were reached sooner with both doses of TX-004HR than with the comparator vaginal tablets (Fig. 3). Estradiol  $t_{max}$  was 1.8 h after 10 µg of TX-004HR versus 9.3 h after 10 µg of the comparator, and the difference was even wider after the 25-µg dose (1.9 versus 11.2 h, respectively).

Estradiol PK parameters in another study were shown to be similar between women's activity levels [16], which may provide more flexibility within their dosing regimen. Concentrations,  $C_{max}$ , and  $AUC_{0-24}$  for estradiol were not different between women who were ambulatory or supine for 4 h following TX-004HR administration.

## 3.2. Estradiol absorption with TX-004HR versus placebo: phase 3 REJOICE study

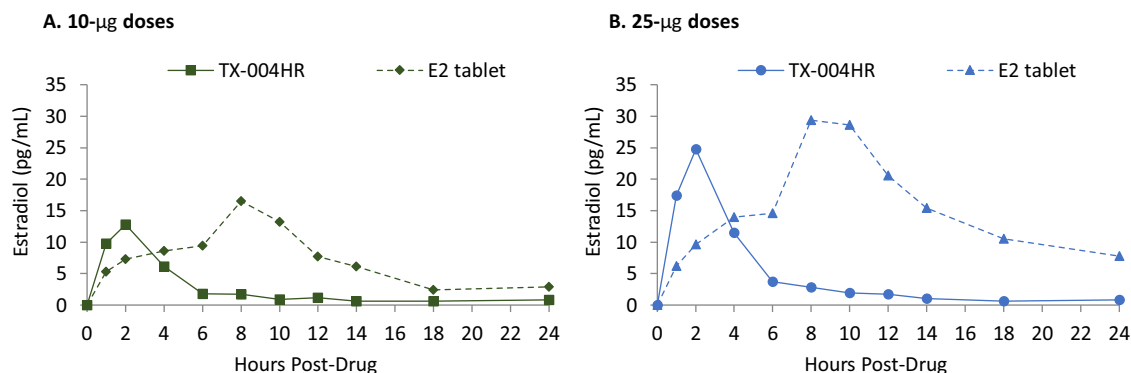
### 3.2.1. Study design and participants

The PK substudy of the REJOICE trial evaluated short-term (2 weeks) and long-term (day 84) systemic exposure of estradiol after daily administration of three TX-004HR doses (4 µg, 10 µg, and 25 µg; Table 1) [13]. Estradiol concentrations were assessed by gas chromatography-tandem mass spectrometry in serum samples taken at screening, on days 1 and 14 (up to 24 h after dosing), and on day 84 (single measurement approximately 4 days after last TX-004HR dose). The estradiol LLOQ was 2.0 pg/mL. Primary PK endpoints included estradiol  $AUC_{0-24}$ , average concentration ( $C_{avg}$ ),  $C_{max}$ , and  $t_{max}$  on days 1 and 14. Mean estradiol concentration on day 84 was examined to determine drug accumulation after twice-weekly chronic TX-004HR treatment.

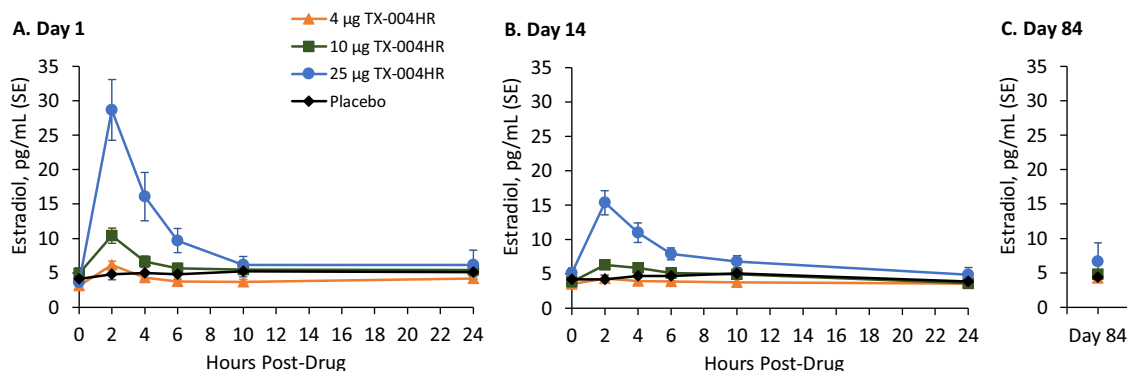
Enrollment criteria are explained above (section 2.2.2). Of the 764 women randomized in the main REJOICE study (Fig. 1), 72 women from 11 study sites that had the ability to perform PK sampling were eligible for the PK substudy, in which they were randomized to TX-004HR 4 µg ( $n = 18$ ), 10 µg ( $n = 19$ ), or 25 µg ( $n = 18$ ), or placebo ( $n = 17$ ). One woman taking placebo did not complete the substudy. Mean age was 59 years, mean BMI 28 kg/m<sup>2</sup>, and 94% of women were white.

### 3.2.2. Estradiol absorption

Fig. 4 shows mean estradiol concentrations over time for all TX-004HR doses versus placebo at day 1 (Fig. 4A) and day 14 (Fig. 4B) [13]. For the most part, unadjusted estradiol PK parameters (Table 2) were similar between the 4-µg and 10-µg TX-004HR doses and placebo on days 1 and 14. While the most indicative measures of estradiol exposure,  $AUC$  and  $C_{avg}$ , were similar for 10 µg TX-004HR and placebo on days 1 and 14,  $C_{max}$  was higher



**Fig. 3.** Phase 1 studies: baseline-corrected mean plasma concentration versus time curve for estradiol after treatment with TX-004HR at (A) 10 µg versus comparator, and (B) 25 µg versus comparator.  $AUC_{0-24}$  comparison is significantly different for both doses ( $P < 0.001$ ) [12]. Modified with permission from Pickar et al. Climacteric 2016;19:181–187.



**Fig. 4.** REJOICE trial PK substudy: unadjusted mean serum estradiol concentrations over time after treatment with TX-004HR 4 µg ( $n = 18$ ) 10 µg ( $n = 19$ ), or 25 µg ( $n = 18$ ) versus placebo ( $n = 16$ ) at (A) day 1 and (B) day 14; and on day 84 (approximately 4 h after the last TX-004HR dose) [13].

**Table 2**  
Unadjusted pharmacokinetic parameters for estradiol in the REJOICE study [13].

Parameter	TX-004HR			
	4 µg ( $n = 18$ )	10 µg ( $n = 19$ )	25 µg ( $n = 18$ )	Placebo ( $n = 17$ )
AUC, pg·h/mL				
Day 1	91.7 ± 37.9	138.2 ± 75.2	217.4 ± 99.0 <sup>b</sup>	116.6 ± 77.3
Day 14	87.2 ± 42.8	110.1 ± 54.6	171.6 ± 80.1 <sup>a</sup>	104.2 ± 66.4
$C_{max}$ , pg/mL				
Day 1	6.5 ± 2.1	10.9 ± 5.0 <sup>a</sup>	29.8 ± 17.5 <sup>c</sup>	6.6 ± 4.9
Day 14	4.8 ± 2.3	7.3 ± 2.4	15.7 ± 7.6 <sup>c</sup>	5.5 ± 3.4
$C_{avg}$ , pg/mL				
Day 1	3.9 ± 1.5	5.8 ± 3.1	9.1 ± 4.1 <sup>b</sup>	4.9 ± 3.2
Day 14	3.6 ± 1.8	4.6 ± 2.3	7.1 ± 3.3 <sup>a</sup>	4.3 ± 2.8
$T_{max}$ , h				
Day 1	7.0 ± 9.4	6.1 ± 8.0	4.6 ± 7.1	8.6 ± 6.7
Day 14	9.3 ± 8.9	4.0 ± 2.6 <sup>b</sup>	2.7 ± 1.9 <sup>c</sup>	7.2 ± 3.0

Data are unadjusted for baseline and are represented as mean ± SD.

<sup>a</sup> $P < 0.05$ ; <sup>b</sup> $P < 0.01$ ; <sup>c</sup> $P < 0.001$  vs placebo using  $t$ -tests.

on day 1 versus placebo (but not on day 14) and  $t_{max}$  was lower on day 14 (Table 2). Women taking 25 µg of TX-004HR had significantly higher values than placebo for all PK parameters on both days (Table 2); however, average daily estradiol levels were within the postmenopausal range of women not taking hormones (~20 pg/mL [17,18]).

Estradiol absorption with TX-004HR was generally lower by day 14 than observed on day 1 (Fig. 4), which may be explained by higher estradiol absorption through atrophic vaginal tissues at therapy initiation, and lower absorption as vaginal maturation improves with continued treatment [19]. Estradiol concentrations on day 84 (Fig. 4C) were not significantly different from baseline

or placebo for any TX-004HR groups, suggesting no estradiol accumulation.

#### 4. Discussion

These studies collectively demonstrated that the TX-004HR vaginal softgel estradiol capsule at all doses resulted in better efficacy on objective (vaginal cells and pH) and subjective (VVA symptoms) measures than placebo, with safety similar to placebo and negligible to very low systemic estradiol absorption, in postmenopausal women. In the phase 2 efficacy study and the phase 3 REJOICE study, all TX-004HR doses improved vaginal physiology as early as week 2 and throughout the 12-week phase 3 trial. Vaginal symptoms, including dyspareunia and vaginal dryness, also improved in the phase 3 study as early as week 2, depending on dose. TX-004HR may more rapidly effect VVA symptoms than other local estrogens, however, in studies of other products, effects on symptoms have not been reported/observed earlier than week 12 with conjugated estrogens cream [20], week 3 with synthetic conjugated estrogens cream [21], or weeks 7–8 with a vaginal estradiol tablet [22,23]. These studies did not report individual VVA symptoms at all or not prior to week 12 [20–23]. Further, oral daily ospemifene did not significantly improve dyspareunia [24] or vaginal dryness [25] until week 12.

PK data from the REJOICE trial demonstrated that 4 µg or 10 µg TX-004HR resulted in estradiol levels ( $AUC_{0-24}$  and  $C_{avg}$ ) similar to those of placebo on days 1 and 14, and even though PK parameters with 25 µg were significantly higher versus placebo, average daily estradiol levels remained within the normal postmenopausal range (~20 pg/mL [17,18]). Estradiol absorption was also significantly lower with the 10-µg and 25-µg TX-004HR doses than with

the same doses of the lowest currently available vaginal estradiol tablet in the comparative phase 1 study [12]. When comparing 10 µg and 25 µg TX-004HR with the same doses of the estradiol tablet, total estradiol exposure (AUC<sub>0-24</sub>) was 3-fold lower with TX-004HR, and estradiol C<sub>max</sub> was 1.4-fold and 1.8-fold lower with 10 µg and 25 µg TX-004HR, respectively [12]. Estradiol C<sub>max</sub> was also more than 4-fold and almost 3-fold lower with 10 µg and 25 µg TX-004HR, respectively, than with the 7.5-µg vaginal estradiol ring (C<sub>max</sub> 63.5 pg/mL) over 24 h [26]. In all 3 PK studies, systemic estradiol absorption occurred more rapidly with TX-004HR and returned to baseline levels faster compared with placebo or comparator. Finally, no estradiol accumulation was evident as found by estradiol levels similar to placebo with all TX-004HR doses at day 84. This evidence collectively suggests that, if approved, TX-004HR could potentially have the lowest estradiol absorption profile of currently available local vaginal estrogen therapies. One might hypothesize that minimal systemic absorption may be associated with a better side effect profile than currently available options.

TX-004HR efficacy and PK data together provide support for local vaginal benefits of estradiol in postmenopausal women with limited systemic estradiol exposure, as it was designed. Thus, it may be an attractive option for women who have expressed concern with systemic absorption of vaginal estrogens. Minimal systemic estradiol absorption with TX-004HR could also foster the ability to use a low-dose vaginal estrogen without a progestin, as the North American Menopause Society recommends [7], and to treat vaginal symptoms in estrogen-dependent breast cancer survivors, as the American Congress of Obstetricians and Gynecologists recently recommended [27].

TX-004HR was designed to be easier to use (without an applicator) and have less mess than with creams, which was intended to improve overall user experience and product acceptability and satisfaction. Data from a survey within the REJOICE study, which will be reported in a separate publication, found that most women thought the product was easy to use and insert, and that versus placebo, more women were satisfied with TX-004HR, preferred TX-004HR over their previous treatment, and would consider using TX-004HR again [28]. Finally, women may have more flexibility within the dosing regimen, since estradiol PK was not affected by body position and they can choose any time of the day to initiate therapy.

## 5. Conclusions

TX-004HR provides efficacy across the most common symptoms of VVA, with negligible to very low systemic absorption of estradiol that was also lower than the currently available lowest estradiol dose in a vaginal tablet. TX-004HR may be a safe, effective, and easy-to-use alternative for postmenopausal women with VVA.

## Contributors

All of the authors contributed to the design and concept of the review and writing of the manuscript.

## Conflict of interest

JAS has served (within the last year) or is currently serving as a consultant to or on the advisory boards of: AbbVie Inc, Allergan, AMAG Pharmaceuticals Inc, Amgen Inc, Apotex Inc, Ascend Therapeutics, JDS Therapeutics LLC, Merck, Noven, Novo Nordisk, Nuelle Inc, Perrigo Company PLC, Radius Health, Regeneron Pharmaceuticals Inc, Roivant Sciences Inc, Sanofi S.A., Sermonix Pharmaceuticals, Shionogi Inc, Sprout Pharmaceuticals, Symbiotec Pharmed, TherapeuticsMD, and Valeant Pharmaceu-

ticals; and has also served (within the last year) or is currently serving on the speaker's bureaus of: Amgen Inc, Eisai Inc, Merck, Noven, Novo Nordisk, Shionogi Inc, and Valeant; and in the last year has received or is currently receiving grant/research support from: AbbVie, Actavis, Agile Therapeutics, Bayer Healthcare, New England Research Institute Inc, Novo Nordisk, Palatin Technologies, Symbio Research Inc, and TherapeuticsMD; and is a stockholder (direct purchase) in Sermonix Pharmaceuticals.

DFA (within the past 3 years) has received research support from Actavis (previously Allergan, Watson Pharmaceuticals, Warner Chilcott), Bayer Healthcare, Endoceutics, Glenmark, Merck (previously Schering Plough, Organon), Radius Health, Shionogi Inc, and TherapeuticsMD; has served as consultant to AbbVie (previously Abbott Laboratories), Actavis (previously Allergan, Watson Pharmaceuticals, Warner Chilcott), Agile Therapeutics, Bayer Healthcare, Endoceutics, Exeltis (previously CHEMO), InnoVaGyn, Merck (previously Schering Plough, Organon), Pfizer, Radius Health, Sermonix Pharmaceuticals, Shionogi Inc, Teva Women's Healthcare, and TherapeuticsMD.

GDC consults to multiple pharmaceutical companies, including but not limited to TherapeuticsMD, and has stock options from TherapeuticsMD.

JHP has received consultant fees from Pfizer, Shionogi Inc, Radius Health Inc, and TherapeuticsMD; and has stock options with TherapeuticsMD.

JMA is an employee of TherapeuticsMD with stock/stock options.

BB is a board member and employee of TherapeuticsMD with stock/stock options.

SG is an employee of TherapeuticsMD with stock/stock options.

SM is an employee of TherapeuticsMD with stock/stock options.

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## Ethical approval

All of the reviewed trials, which were sponsored by TherapeuticsMD, were approved by an appropriate institutional review board and all patients provided written informed consent.

## Provenance and peer review

This article has undergone peer review.

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