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REVIEW

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## Estradiol softgel inserts for the treatment of VVA symptoms: an expert opinion

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### ABSTRACT

**Introduction:** Vulvar and vaginal atrophy (VVA) affects up to two thirds of postmenopausal women, with symptoms of vaginal dryness, dyspareunia, and vulvar/vaginal irritation. Despite the availability of various treatments, women express dissatisfaction with their options. An estradiol (E2; 4- $\mu$ g and 10- $\mu$ g) softgel vaginal insert was approved by the Food and Drug Administration (FDA) to treat moderate to severe dyspareunia, a symptom of VVA, due to menopause. These inserts were designed to treat VVA effectively and safely while avoiding some of the drawbacks of other administration methods.

**Areas covered:** This article reviews the physical characteristics and pharmacokinetic data of the E2 softgel vaginal insert. Primary and secondary efficacy endpoints and safety data are reviewed from the pivotal REJOICE trial (NCT02253173), and substudies that explore response rates, changes in vaginal epithelium by visual assessment, efficacy in patient subgroups, effects on sexual function, and patient satisfaction compared with other treatments.

**Expert opinion:** The E2 insert shows that vaginal drug delivery is an optimal route of administration for locally treating VVA. This E2 softgel vaginal insert is a safe and effective treatment for symptoms of postmenopausal VVA. The E2 insert's pharmacokinetic characteristics are related to its unique formulation, rapid dissolution, and minimal systemic absorption.

**Abbreviations:** AE: adverse event; AUC: area under the concentration-time curve; BMI: body mass index; C<sub>avg</sub>: average concentration; CI: confidence interval; C<sub>max</sub>: maximum concentration; C<sub>min</sub>: minimum concentration; E2: estradiol; FDA: Food and Drug Administration; FSFI: Female Sexual Function Index; GSM: genitourinary symptoms of menopause; MBS: most bothersome symptom; NAMS: North American Menopause Society; OR: odds ratio; PI: pulsatility index; PK: pharmacokinetic; REVIVE: Real Women's Views of treatment options for menopausal Vaginal changEs; RI: resistance index; ROC: receiver operating characteristic; TEAE: treatment-emergent adverse event; t<sub>max</sub>: time to maximum concentration; VVA: vulvar and vaginal atrophy.

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Dyspareunia; estradiol; menopause; softgel vaginal insert; vaginal dryness; vulvar and vaginal atrophy

## 1. Introduction

Approximately half to two thirds of all postmenopausal women experience vulvar and vaginal atrophy (VVA), a component of the genitourinary syndrome of menopause (GSM), which is due to declining serum levels of estrogen and other sex steroids [1–4]. Symptoms including vaginal dryness, dyspareunia, and vulvar/vaginal irritation are progressive and can impair quality of life, including sexual function [5–7]. Despite available treatments, only 40% of women use any VVA-specific therapies, and even fewer (7%) employ prescription-only treatments [5]; reasons for non-treatment include safety concerns, poor efficacy, and dissatisfaction with application procedures (e.g., disruptiveness, messiness) [1,5]. After the publication of the Women's Health Initiative (WHI) results in 2002, which documented elevated risks of heart disease, stroke, pulmonary embolism, and breast cancer with oral hormone therapy [8], the use of oral hormone therapy declined by approximately 80% by 2009 [9]. Use of vaginal therapies increased during the same interval from 20% to 100%,

depending on the age category studied [9]. To treat VVA, the North American Menopause Society (NAMS) recommends the vaginal administration of low-dose estrogen for women who did not respond to nonhormonal interventions such as vaginal moisturizers, because of a lower risk profile compared with systemic estrogen therapy [6].

Vaginal drug delivery allows self-administration, can provide a localized therapeutic effect, avoids gastrointestinal absorption and the hepatic first-pass effect, allows administration of lower doses (versus oral route), and can avoid some adverse effects (e.g., gastric irritation), all of which can enhance treatment compliance [10,11]. Absorption of estradiol delivered vaginally is dose-dependent, and may be influenced by dose, formulation, and positioning in the vagina [12,13].

This article focuses on the development of an ultra-low-dose estrogen for vaginal delivery for the treatment of local symptoms, specifically an E2 softgel vaginal insert for the treatment of moderate to severe dyspareunia due to VVA. Data documenting the efficacy, safety profile, and

**Article highlights**

- Vulvar and vaginal atrophy (VVA) affects up to two thirds of postmenopausal women, with symptoms of vaginal dryness, dyspareunia, and vulvar/vaginal irritation.
- A low-dose estradiol (E2) softgel vaginal insert for VVA was designed to achieve rapid local effect, minimal systemic absorption, avoidance of the uterine first pass, with no applicator.
- The vaginal inserts (4, 10, and 25 µg E2) significantly improved percentages of parabasal, and superficial vaginal cells; vaginal pH; and VVA symptoms of dyspareunia and vaginal dryness (primary efficacy endpoints; vaginal dryness was a secondary endpoint) versus placebo from baseline, with an onset of action achieved within 2 weeks for most endpoints.
- Improvements in sexual function, good patient satisfaction, and minimal vaginal discharge during administration were also observed.
- The E2 softgel vaginal insert had similar rates of adverse events compared with placebo with no cases of endometrial hyperplasia or malignancy.

This box summarizes key points contained in the article.

minimal systemic absorption with the E2 softgel vaginal insert are also reviewed.

## 2. Estradiol softgel vaginal insert

### 2.1. Physical characteristics

The E2 softgel vaginal insert (TX-004 HR, Imvexxy® [estradiol vaginal inserts]; TherapeuticsMD, Boca Raton, FL) is approved by the FDA at dosages of 4 µg and 10 µg for the treatment of moderate to severe dyspareunia, a symptom of VVA due to menopause [14]. The E2 vaginal inserts are small, light-pink, tear-shaped softgel capsules, which are inserted manually without the use of an applicator in the lower part of the vagina [15]. The outer capsule shell is composed of gelatin polymers to impart mucoadhesive properties and aid in the retention of the capsule in the vagina while allowing fast dissolution and quick release of the medication in the vagina, and complete dissolution by 6 hours after insertion [15].

### 2.2. Primary efficacy data

Menopause is characterized by recognizable changes in vaginal epithelial cytology, including a decrease in superficial and intermediate cells and an increase in parabasal cells, in contrast to the premenopausal state. The vaginal mucosa comprises 4 cellular layers, which are stratified squamous epithelium, elastic lamina propria, fibromuscular layer, and adventitia. A biofilm coats the vaginal epithelium in premenopausal women but is less evident in postmenopausal women [6]. Thinning of the epithelium during menopause facilitates drug delivery into the deeper tissue layers [6]. Vaginal pH is typically less acidic in menopause and increases above 5.0. All of these changes are associated with symptoms of VVA [6], so improvements in these parameters can demonstrate the efficacy of vaginally administered treatments for VVA symptoms.

The efficacy of the E2 softgel vaginal insert (TX-004 HR) was evaluated in the REJOICE trial (NCT02253173), a large multicenter, double-blind, randomized, placebo-controlled phase 3 trial, for the treatment of moderate to severe dyspareunia due to VVA [16]. The trial was conducted at 89 sites in the United States and Canada [16]. Participants were healthy postmenopausal women (40 to 75 years) who had ≤ 5% superficial cells on vaginal cytologic smear, vaginal pH > 5.0, moderate to severe dyspareunia as their most bothersome symptom (MBS) that began during postmenopause, body mass index (BMI) ≤ 38 kg/m<sup>2</sup>, and expectation of sexual activity (with vaginal penetration) during the trial [16].

A total of 764 women were randomized to receive the E2 vaginal insert (TX-004 HR) 4 µg, 10 µg, or 25 µg, or matching placebo for vaginal insertion, without the use of an applicator, once daily for 2 weeks and then twice weekly for 10 weeks [16]. Each treatment dosage was compared with placebo for changes between baseline and week 12 for 4 co-primary efficacy endpoints: (1) percentage of vaginal superficial cells, (2) percentage of vaginal parabasal cells, (3) vaginal pH, and (4) severity of dyspareunia [16]. Secondary endpoints included changes in the severity of vaginal dryness and vulvar and/or vaginal itching or irritation [16]. The severity of VVA symptoms was rated using a 4-point scale (0 = none; 1 = mild; 2 = moderate; and 3 = severe) [16].

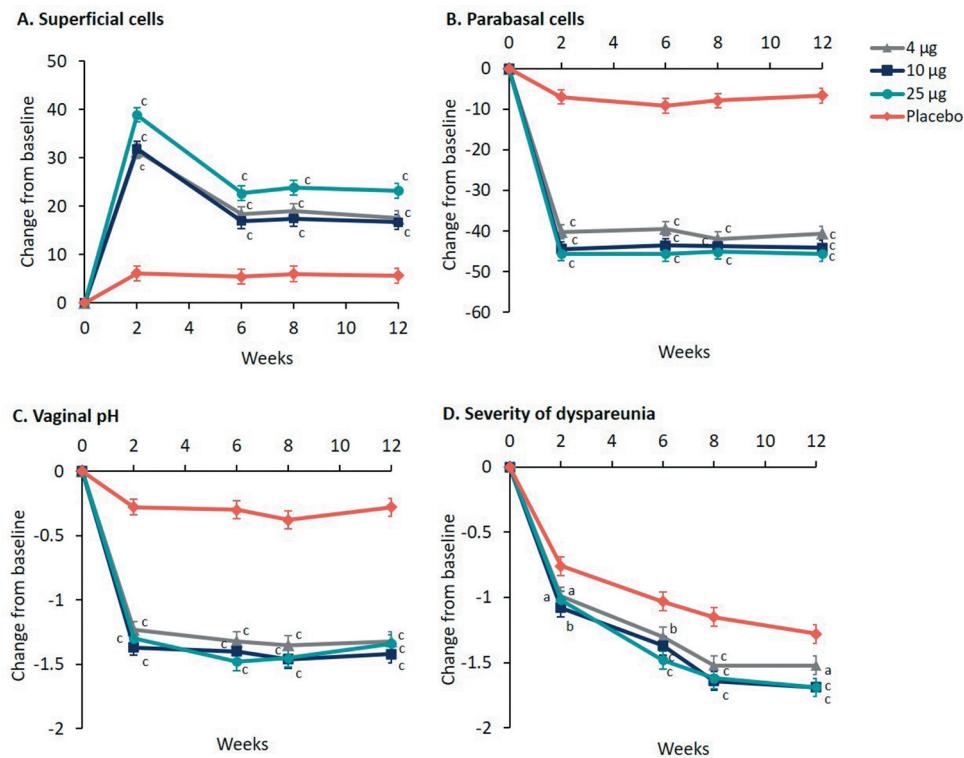
All 4 co-primary endpoints significantly improved at week 12 with all three E2 doses versus placebo, with significant improvements occurring as early as week 2 (Figure 1) [16]. Superficial cells increased by 17–23% with the E2 inserts versus 6% with placebo, and parabasal cells decreased by 41–46% with E2 versus 7% with placebo [16]. Treatment with all E2 doses significantly improved dyspareunia from baseline as early as week 2 [16]. Early onset of action at 2 weeks (change in vaginal pH and in the percentage of parabasal, superficial, and intermediate cells) was also observed in a phase 2 trial, which evaluated daily 10-µg E2 TX-004 HR or matching placebo for 2 weeks in 48 postmenopausal women [17].

Significant improvements from baseline compared with placebo were also observed for secondary efficacy outcomes in REJOICE; vaginal dryness significantly improved with all E2 doses, and vulvar and/or vaginal itching or irritation significantly improved with the 10-µg and 25-µg E2 doses at week 12 [16].

### 2.3. Other efficacy analyses

#### 2.3.1. Subgroup analyses

Subgroup analyses (secondary endpoints) were performed to determine if age (≤ 56, 57–61, and ≥ 62 years), BMI (≤ 24, 25–28, and ≥ 29 kg/m<sup>2</sup>), uterine status (intact uterus or no intact uterus), pregnancy history (0 or ≥ 1), or number of vaginal births (0 or ≥ 1) had any effects on treatment outcomes (percentages of superficial and parabasal cells, vaginal pH, and severity of dyspareunia or vaginal dryness [19]) [20]. Descriptive analyses



**Figure 1.** 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 [16]. <sup>a</sup>p < 0.05, <sup>b</sup>p < 0.01, <sup>c</sup>p < 0.001 for TX-004 HR versus placebo. Figure modified from Simon et al 2017 [18].

were used because the REJOICE study was not powered to evaluate these secondary endpoints [19,20].

At baseline, the percentage of parabasal cells and vaginal pH were positively correlated with age and inversely correlated with BMI (all,  $p \leq 0.002$ ). Overall, treatment effects observed with the E2 inserts compared with placebo occurred regardless of age, BMI, uterine status, pregnancy history, and previous vaginal births, with most subgroup comparisons being statistically significant at weeks 2 and 12 [19,20].

### 2.3.2. Response rates

Response rates were also analyzed with responders defined a priori as women meeting at least 2 out of 3 clinical endpoints: vaginal superficial cells  $> 5\%$ , vaginal pH  $< 5.0$ , and improvement from baseline in dyspareunia of  $\geq 1$  category (eg, rating of moderate to mild) [21].

Significantly higher response rates were observed with the three E2 doses than with placebo at week 2 (74, 81, and 82%, respectively, vs 24% for placebo; all,  $p < 0.0001$ ) and week 12 (72, 80, and 79%, respectively, vs 33% for placebo; all,  $p < 0.0001$ ) [21]. Likelihood of being a responder with treatment versus placebo was 9- to 14-fold higher for the three E2 doses (ORs 8.8, 13.7, and 14.4) at week 2, and 5- to 8-fold higher at week 12 (ORs 5.4, 8.4, and 7.6) [21]. Overall responder rates for the E2 inserts were similar

at week 2 (79.5%) and week 12 (78.4%). Of those who responded at week 2, 85% responded at week 12; while of the 20.5% who were non-responders at week 2, 46% were responders at week 12 [21]. Response at week 2 with E2 was highly predictive of response at week 12 (OR 7.9; 95% CI, 4.7–13.2) [21].

### 2.3.3. Meaningful improvements of VVA symptoms

Meaningful improvements in the VVA symptoms of dyspareunia and vaginal dryness were also evaluated ( $n = 704$ ) [19]. Post hoc analyses examined the percentages of women with 'substantial' symptom ( $\geq 2$  point) improvement, 'complete resolution' (score = 0), and 'clinically meaningful' ( $\geq 1$  point) improvement for both dyspareunia and vaginal dryness; as well as predictors of improvement in vaginal dryness (concurrent with dyspareunia) [19].

For dyspareunia, significantly higher rates of substantial improvement were observed at week 12 with each E2 dose (41–55%) versus placebo (34%); and the two higher doses achieved significantly higher rates of complete resolution (32% and 31% vs placebo 20%) [19]. Similar results were observed for vaginal dryness, with significant substantial improvement observed at week 12 with each E2 dose compared with placebo (41–51% vs 31%) and significantly higher rates of complete resolution with all E2 doses (31–38% vs 16%) [19]. Approximately, 80% of women receiving any E2

dose had clinically meaningful improvement in both symptoms ( $p < 0.05$ ) [19].

#### 2.3.4. Visual assessment

Visual assessment of changes in the vaginal epithelium ( $n = 704$ ) evaluated with treatment and in relation to VVA symptoms was another secondary endpoint of the REJOICE trial [22]. Examinations were performed using a 4-point scale (from 0 = none to 3 = severe) to assess vaginal color, vaginal epithelial integrity, vaginal epithelial surface thickness, and vaginal secretions [22].

All vaginal assessment parameters significantly improved from baseline to week 12 with all E2 doses versus placebo (Table 1) [22]. Significantly more women using E2 had severity ratings of none to mild at week 12; vaginal color (79– 84% vs 65% for placebo), vaginal epithelial integrity (83– 89% vs 71%), vaginal epithelial surface thickness (78– 83% vs 55%), and vaginal secretions (80– 83% vs 61%) (all,  $p \leq 0.0001$  for each dose). All of these significant improvements were evident by week 2 [22]. Further, the sum of the individual visual assessment scores showed a significant linear correlation with the severity of dyspareunia and vaginal dryness at week 12 (both,  $p < 0.0001$ ) [22]. Visual assessment appeared to be a useful means of diagnosing VVA and evaluating treatment response [22].

#### 2.4. Effect on sexual function

Some studies have shown that VVA symptoms have a negative impact on women's sexual function, with 58% to 85% of women reporting loss of intimacy, loss of libido, dyspareunia, and avoidance of intimacy as a result [5,7]. In the REJOICE trial, sexual function ( $n = 692$ ) [23] was assessed using the Female Sexual Function Index (FSFI), a validated self-report instrument categorized into 6

domains (desire, arousal, lubrication, orgasm, satisfaction, and pain), which measures symptoms over the past 4 weeks [24].

All study groups including placebo showed numerical improvements in total FSFI and individual domain scores from baseline to week 12, although several comparisons were significantly greater with the E2 inserts than with placebo [23]. For the total FSFI score, significant improvements were observed for the 10- $\mu$ g and 25- $\mu$ g doses versus placebo [23]. The two higher dose groups also had numerically better scores than placebo for all FSFI domains [23]. Significant improvements compared with placebo were observed for the lubrication and pain domains for the 10- $\mu$ g and 25- $\mu$ g doses, and for the arousal and satisfaction domains for the 25- $\mu$ g dose [23].

#### 2.5. Satisfaction

Despite the efficacy and safety of various vaginal estrogen therapies for VVA, studies document women's concerns related to route of administration, lack of convenience, and safety regarding systemic exposure and long-term use [5,25–27]. Women surveyed in the REVIVE trial (Real Women's Views of treatment options for menopausal Vaginal changEs) cited several disadvantages of over-the-counter vaginal moisturizers and lubricants, prescription vaginal products, and vaginal creams, including difficulty administering the correct dose, inconvenience, and messiness, and incomplete effectiveness [5,26]. Vaginal rings can change position or dislodge [6], and women using them have reported difficulty with insertion and removal and concerns about infection and hygiene [25]. As a result, up to half (21% to 50%) of women have reported being dissatisfied with the currently available vaginal estrogen therapies [23,28]. Compliance with proper dosing is poor [26],

**Table 1.** Visual assessments in the REJOICE trial: LS mean change from baseline to weeks 2 and 12 [22].

Vaginal Parameters		TX-004 HR 4 $\mu$ g		TX-004 HR 10 $\mu$ g		TX-004 HR 25 $\mu$ g		Placebo
<b>Vaginal color</b>	n		n		n		n	
Baseline score, mean $\pm$ SD	186	1.8 $\pm$ 0.61	188	1.7 $\pm$ 0.59	186	1.8 $\pm$ 0.60	187	1.7 $\pm$ 0.64
LS Mean (SE)								
Week 2	185	-0.69 (0.05) <sup>b</sup>	187	-0.77 (0.05) <sup>b</sup>	184	-0.78 (0.05) <sup>b</sup>	186	-0.40 (0.05)
Week 12	171	-0.97 (0.05) <sup>b</sup>	173	-1.06 (0.05) <sup>b</sup>	175	-0.96 (0.05) <sup>b</sup>	175	-0.60 (0.05)
<b>Vaginal epithelial integrity</b>	n		n		n		n	
Baseline score, mean $\pm$ SD	186	1.6 $\pm$ 0.84	188	1.4 $\pm$ 0.83	186	1.5 $\pm$ 0.77	187	1.5 $\pm$ 0.84
LS Mean (SE)								
Week 2	185	-0.85 (0.05) <sup>b</sup>	187	-0.87 (0.05) <sup>b</sup>	184	-0.93 (0.05) <sup>b</sup>	186	-0.53 (0.05)
Week 12	171	-0.97 (0.05) <sup>b</sup>	173	-1.07 (0.05) <sup>b</sup>	175	-1.01 (0.05) <sup>b</sup>	175	-0.60 (0.05)
<b>Vaginal epithelial surface thickness</b>	n		n		n		n	
Baseline score, mean $\pm$ SD	186	1.9 $\pm$ 0.67	188	1.8 $\pm$ 0.63	186	1.9 $\pm$ 0.59	187	1.9 $\pm$ 0.65
LS Mean (SE)								
Week 2	185	-0.76 (0.05) <sup>b</sup>	187	-0.76 (0.05) <sup>b</sup>	184	-0.76 (0.05) <sup>b</sup>	186	-0.40 (0.05)
Week 12	171	-0.98 (0.05) <sup>b</sup>	173	-1.03 (0.05) <sup>b</sup>	175	-0.94 (0.05) <sup>b</sup>	175	-0.61 (0.05)
<b>Vaginal secretions</b>	n		n		n		n	
Baseline score, mean $\pm$ SD	186	1.8 $\pm$ 0.68	188	1.7 $\pm$ 0.66	186	1.7 $\pm$ 0.63	187	1.8 $\pm$ 0.63
LS Mean (SE)								
Week 2	185	-0.79 (0.05) <sup>a</sup>	187	-0.83 (0.05) <sup>b</sup>	184	-0.86 (0.05) <sup>b</sup>	186	-0.54 (0.05)
Week 12	171	-1.01 (0.05) <sup>b</sup>	173	-1.06 (0.05) <sup>b</sup>	175	-1.04 (0.05) <sup>b</sup>	175	-0.64 (0.05)

LS: least square; SD: standard deviation; SE: standard error.

<sup>a</sup> $p < 0.001$ ; <sup>b</sup> $p < 0.0001$  vs placebo.

and most women discontinue prescription treatments prematurely, within 45 days for vaginal creams and 103 days for vaginal tablets [29]. Women cited safety concerns, side effects, administration difficulties, messiness, and questionable efficacy as reasons why 38% chose not to refill prescriptions [27].

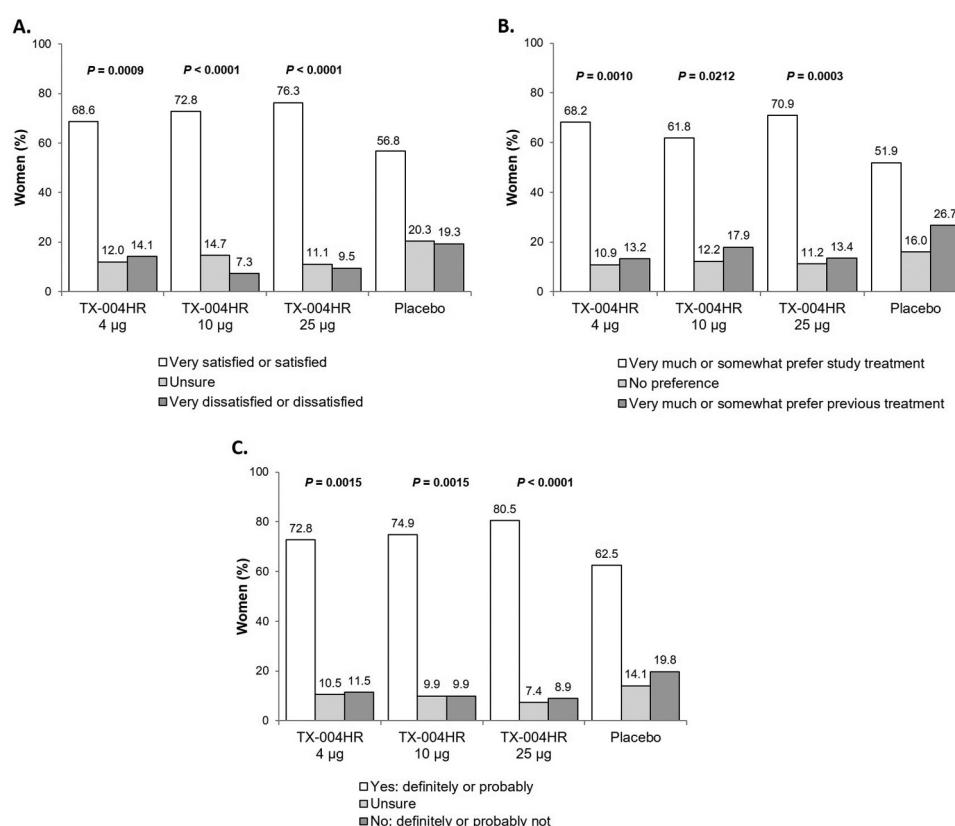
Patient satisfaction was assessed using a 5-question acceptability questionnaire on the ease of use and satisfaction with the vaginal inserts [30]. Most women in all groups found the product easy to use (85 to 92%) and rated the ease of capsule insertion as 'good' or 'excellent' (75 to 83%) [30]. Ease of capsule insertion was significantly associated with decreases in dyspareunia and vaginal dryness severity (both,  $p < 0.0001$ ) [30]. Significantly more women were 'very satisfied or satisfied' with the E2 insert versus placebo (Figure 2a), with satisfaction being inversely correlated with dyspareunia, vaginal dryness, percentage of vaginal superficial cells, and vaginal pH (all,  $p \leq 0.0002$ ) [30]. Women also preferred the E2 softgel vaginal insert to treatments they had used before (Figure 2b) and would 'probably' or 'definitely' use the product again relative to placebo (Figure 2c) [30]. Changes in dyspareunia and vaginal dryness were correlated with the likelihood to use the E2 softgel vaginal insert again (both,  $p < 0.0001$ ) [30].

## 2.6. Pharmacokinetic data

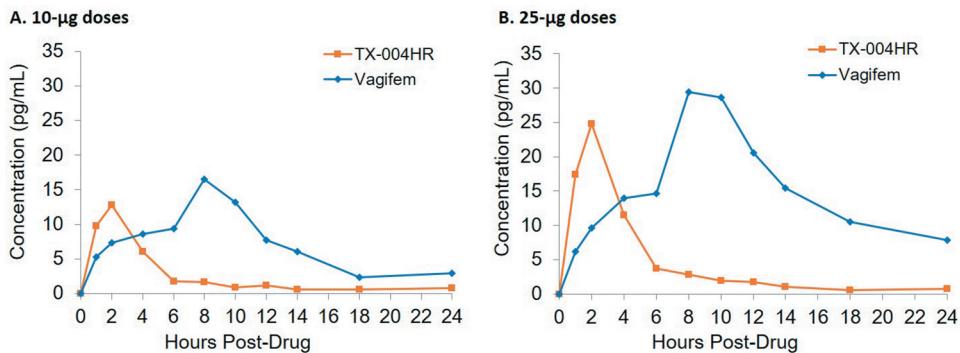
Three pharmacokinetic (PK) studies document minimal systemic absorption of E2 with vaginal administration of the E2 softgel vaginal insert [31,32].

Two randomized, open-label, single-dose, 2-way crossover studies evaluated the relative bioavailability and safety of the E2 softgel vaginal insert (test product; TX-004 HR) versus an approved E2 tablet vaginal insert (reference drug; Vagifem) [31]. In each study (one for the 10- $\mu\text{g}$  E2 dose and one for the 25- $\mu\text{g}$  E2 dose), healthy postmenopausal women ( $n = 35$ ) aged 40 to 65 years were randomly assigned to the vaginal insert or tablet [31]. Outcomes were area under the concentration-time curve from 0 to 24 h ( $\text{AUC}_{0-24}$ ) and maximum concentration ( $C_{\max}$ ) for E2, estrone, and estrone sulfate; as well as relative bioavailability of the softgel vaginal insert at doses of 10  $\mu\text{g}$  and 25  $\mu\text{g}$  versus the reference drug [31]. All serum E2 measurements were performed using a highly specific and ultrasensitive liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay [31].

Overall, the results indicated lower systemic exposure with the E2 softgel vaginal insert than with the vaginal tablet comparator (Figure 3; Table 2) [31]. A follow up of this PK study also demonstrated that there were no body position effects (supine vs ambulatory/seated) on the E2 bioavailability with the TX-004 HR inserts [15].



**Figure 2.** Women's (a) satisfaction with TX-004 HR; (b) likelihood of using TX-004 HR again; (c) treatment preference over previously used vulvar and vaginal atrophy treatments. P-value vs placebo. Figure modified from Kingsberg et al, 2017 [30].



**Figure 3.** Phase 2 studies: baseline-corrected mean plasma concentration versus time curve for estradiol after treatment with TX-004 HR (a) 10 µg and (b) 25 µg versus comparator. AUC<sub>0-24</sub> comparison is significantly different for both doses ( $p < 0.001$ ). Figure modified from Pickar et al, 2017 [31].

**Table 2.** Mean estrogen values in pharmacokinetic trials and ANOVA results for comparisons between TX-004 HR (TherapeuticsMD, Boca Raton, FL) and Vagifem (Novo Nordisk, Plainsboro, NJ) [31].

Dose (µg)	AUC <sub>0-24</sub> (pg·hr/mL)				C <sub>max</sub> (pg/mL)				t <sub>max</sub> (hr)	
	TX-004 HR	Vagifem	p-value	Ratio*	TX-004 HR	Vagifem	p-value	Ratio*	TX-004 HR	Vagifem
Estradiol	49.62	132.92	< 0.0001	38%	14.38	20.38	0.0194	72%	1.75	9.28
10	89.21	292.1	< 0.0001	31%	23.08	42.70	< 0.0001	54%	1.85	11.18
25										
Estrone	24.24	48.24	0.0002	46%	5.15	6.98	0.0127	75%	5.87	9.07
10	50.22	165.5	< 0.0001	31%	10.69	23.58	0.0002	51%	5.14	11.48
25										
Estrone sulfate	66.6 (ng·hr/dL)	121.6 (ng·hr/dL)	0.0091	67%	12.2 (ng/dL)	16.9 (ng/dL)	0.0366	75%	5.5	8.8
10	4290	7330	0.0031	58%	(ng/dL)	(ng/dL)	0.0042	58%	11.75	15.87
25					497.6	730.6				

Data represented as baseline adjusted geometric mean. \*Ratio of TX-004 HR to Vagifem. P-values between TX-004 HR and Vagifem

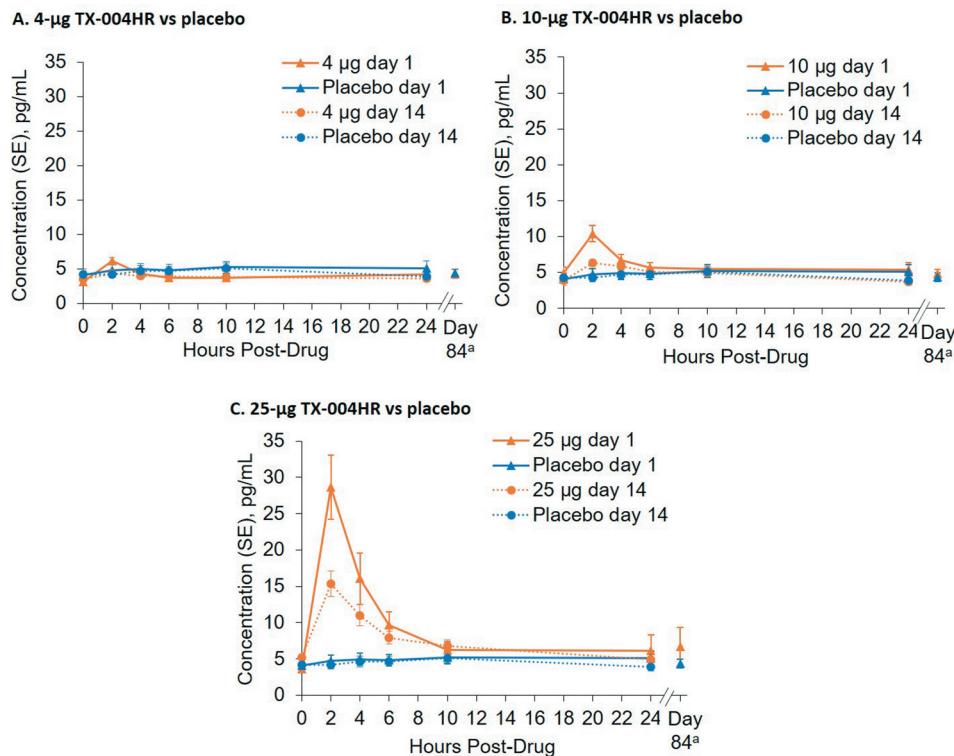
Finally, the PK parameters for TX-004 HR were evaluated in a substudy of the REJOICE trial [32]. Women in the PK substudy ( $n = 72$ ) were randomized separately from the main phase 3 study in a 1:1:1:1 ratio to receive the 4-, 10-, or 25-µg E2 softgel vaginal insert, or matching placebo, self-administered once daily for 2 weeks and then twice weekly for 10 weeks [32].

Serum E2 concentrations over time with treatment are shown in Figure 4 [32]. No significant differences were observed between the 4-µg E2 dose and placebo for E2 AUC, C<sub>max</sub>, average concentration (C<sub>avg</sub>), minimum concentration (C<sub>min</sub>), or t<sub>max</sub>. A significant difference was observed between the 10-µg dose and placebo only for C<sub>max</sub> on day 1 (10.9 vs 6.6 pg/mL;  $p < 0.05$ ), but no significant difference was found on day 14 [32]. With the 25-µg dose, treatment on day 1 was associated with significantly higher AUC (217.4 vs 116.6 pg·h/mL), C<sub>max</sub> (29.8 vs 6.6 pg/mL), and C<sub>avg</sub> (9.1 vs 4.9 pg/mL) (all,  $p < 0.01$ ); differences were smaller on day 14 but remained significant [32]. E2 concentrations on day 84 (three days following the final dose) were similar to baseline and placebo for all E2 groups, suggesting no systemic accumulation of E2 [32]. None of the PK results for estrone and estrone conjugate were elevated versus

placebo at any dose [32]. Overall, this study showed that average levels of E2 remained within the postmenopausal range with the 4-µg and 10-µg dose (i.e.,  $\leq 20$  pg/mL) [32].

## 2.7. Primary safety data

Safety results of the REJOICE trial showed that the E2 softgel insert was well tolerated, with no clinically significant differences in adverse events (AEs) between treatment and placebo [16]. Headache was the only drug-related TEAE that was numerically more frequent with active treatment (3.7% for 4-µg dose vs 3.1% for placebo) [16]. Notably, rates of vaginal discharge were lower in all treatment groups (2.1 to 3.1%) compared with placebo (6.8%) [16]. Most TEAEs were mild to moderate in severity, and only 1.8% of participants discontinued because of AEs [16]. None of the serious TEAEs were considered related to treatment and there were no deaths. No cases of endometrial proliferation, hyperplasia, or malignancy in endometrial biopsies were found up to week 12, and changes in sex hormone-binding globulin in evaluable women ( $n = 72$ ) were not significant with E2 versus placebo [16].



**Figure 4.** REJOICE trial PK substudy: unadjusted mean serum estradiol concentrations over time after treatment with TX-004 HR (A) 4 µg (n = 18), (B) 10 µg (n = 19), or (C) 25 µg (n = 18) versus placebo (n = 16) at days 1, 14, and 84 (approximately 4 h after the last TX-004 HR dose); <sup>a</sup>4 days post-dosing. Figure modified from Archer et al, 2017 [32].

## 2.8. Study limitations

The REJOICE trial had several limitations, including narrowly-defined inclusion criteria that required women to have signs of VVA (vaginal pH >5.0 and ≤5% superficial cells), as well as moderate to severe dyspareunia as their most bothersome symptom [16]. However, postmenopausal women who suffer from VVA often experience other symptoms than just dyspareunia including vaginal dryness, vaginal irritation, and vaginal itching [16]. Finally, the population evaluated in the REJOICE study might not have been a good representation of the US population, because most women were white, in good health, and had an average BMI of 26.7 kg/m<sup>2</sup> [16].

## 3. Conclusion

A low-dose E2 softgel vaginal insert for VVA was designed to achieve rapid (within 2 weeks) local effect, with minimal systemic hormone exposure, and no need for an applicator. In clinical studies, the E2 softgel vaginal insert versus placebo significantly improved percentages of parabasal and superficial vaginal cells; vaginal pH; and severity of dyspareunia and vaginal dryness for up to 12 weeks. Evidence indicates an onset of action within 2 weeks, improvements in the vaginal epithelium by visual assessment, consistent efficacy in patient subgroups, improvements in sexual function, and good patient satisfaction. Adverse effects were not

significantly different from placebo, and there were no cases of endometrial hyperplasia or malignancy. The data suggest that the E2 softgel vaginal insert is a safe, effective, and well-accepted option for treating postmenopausal women with moderate to severe dyspareunia due to VVA.

## 4. Expert opinion

Clinical studies demonstrate that E2 delivered to the lower vagina via a softgel capsule has primarily local effects. Preliminary results demonstrate that molecular markers of uterine endometrial proliferation (i.e., cellular mitosis/estrogen receptor/progesterone receptor upregulation) are not altered during local administration of the E2 softgel capsule. Additional factors may influence absorption of E2 placed in the lower vagina. These include overall thickness of the vaginal mucosa influenced by previous estrogen milieu and the presence of biofilms created by the vaginal microbiome [33,34], which can affect absorption of the active drug. These factors have not been fully characterized.

The upper vagina is endowed with a rich complex network of capillaries that could be utilized for drug delivery with elimination of the intestinal-hepatic first pass effect metabolism. In this area of research, vaginal mucoadhesive drug delivery systems with microencapsulation technologies are undergoing development [35]. Drugs that are not readily permeable through the vaginal mucosa (ie, polar compounds)

can be driven through the mucosa with the use of permeation enhancers and carriers [36]. These are relatively unexplored areas for future research.

These and other biological properties of the vaginal route for drug delivery are being expanded as our understanding of the biomechanics of drug delivery continues to grow.

These two low-dose (4 µg and 10 µg) vaginal inserts offer a novel treatment option for women with VVA. This use is in line with NAMS recommendations, which state that estrogen vaginally at a low dose (when VVA is the sole condition) remains the therapeutic standard for symptomatic women with moderate to severe VVA and those with milder VVA who do not respond to lubricants and moisturizers [6]. Furthermore, these two doses facilitate the individualization of therapy.

The low-dose vaginal inserts described here may also be of interest to women who are concerned with systemic absorption of locally applied estrogens, such as those at risk of VTEs or breast cancer [6]. Dyspareunia and vaginal dryness are common complaints of breast cancer survivors using adjuvant therapy with aromatase inhibitors or tamoxifen [37–39]. As suggested by NAMS, patients with breast cancer who do not respond to nonhormonal therapies may benefit from having a short-course of low-dose vaginal estrogen therapy to allow resumption of sexual activity [6]. The American College of Obstetricians and Gynecologists (ACOG) also states that vaginal estrogen is the therapy of choice for women with a history of estrogen-dependent breast cancer who are experiencing urogenital symptoms and are unresponsive to nonhormonal remedies [40]. This recommendation is based on all available data, which do not show an increased risk of cancer recurrence in women who are currently undergoing treatment for breast cancer or in those with a personal history of breast cancer who use vaginal estrogen to relieve urogenital symptoms [40]. Additionally, ACOG indicates that when the decision is made to use vaginal estrogen, it should be prescribed at the lowest dose to affect vaginal symptoms [40]. Supporting the use of these low-dose (4-µg and 10-µg E2) vaginal inserts are the results of the PK study, which showed that average systemic levels of E2 remained within the postmenopausal range with use of these inserts [32].

Other local vaginal estrogen products used for the treatment of VVA symptoms include an E2 vaginal tablet insert (10 µg) [41], E2 cream (100 µg/g) [42], a conjugated estrogens cream (0.625 mg) [43], and an E2 vaginal ring (7.5 µg/day), although systemic E2 absorption was observed with the ring[44]. All these products have a much higher dosage and higher systemic absorption compared with the vaginal softgel capsule [12]. Another bioidentical option for the treatment of symptomatic VVA is estriol, although not commercially available in the US. While estriol may be a good choice for some women, the low-dose E2 vaginal inserts (4 µg and 10 µg), that are well studied and FDA-approved, may

be a better option for other women who prefer a bioidentical formulation.

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## Declaration of interest

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