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TX-004HR Improves Sexual Function as Measured by the Female Sexual Function Index in Postmenopausal Women With Vulvar and Vaginal Atrophy: The REJOICE Trial

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ABSTRACT

Introduction: TX-004HR is an investigational, applicator-free, vaginal soft gel capsule containing low-dose solubilized 17β-estradiol. The phase 3, randomized, double-blinded, placebo-controlled, multicenter REJOICE trial has shown TX-004HR to be safe and effective for the treatment of moderate to severe dyspareunia in postmenopausal women with vulvar and vaginal atrophy (VVA).

Aim: To evaluate the effect of TX-004HR on female sexual dysfunction in postmenopausal women with VVA.

Methods: The REJOICE study compared the effects of 12-week treatment with TX-004HR (4, 10, or 25 μg) with placebo in postmenopausal women (40−75 years old) with VVA and a most bothersome symptom of moderate to severe dyspareunia. Changes in the percentage of superficial and parabasal cells, vaginal pH, and dyspareunia were measured as co-primary end points. Female sexual dysfunction was evaluated as a secondary end point using the Female Sexual Function Index (FSFI) patient self-report inventory.

Main Outcome Measures: Changes from baseline to week 12 in total and individual domain FSFI scores for each TX-004HR dose were compared with those for placebo.

Results: All three TX-004HR doses increased the baseline total FSFI score after 12 weeks, with 10 μg ($P < .05$) and 25 μg ($P = .0019$) having a significantly greater effect than placebo. A similar trend was observed for the individual FSFI domains, with 10 and 25 μg significantly improving baselines scores for pain and lubrication at 12 weeks ($P \leq .015$ for all vs placebo). Changes from baseline to week 12 in arousal ($P = .0085$) and satisfaction ($P = .0073$) were significantly greater for TX-004HR 25 μg vs placebo. All three TX-004HR doses were comparable to placebo in their effect on desire and orgasm.

Conclusion: TX-004HR improved FSFI scores in a dose-dependent manner. The observed improvements in sexual function suggest that TX-004HR is a promising treatment option for postmenopausal VVA with a potential added beneficial effect on female sexual dysfunction.

Key Words: Estradiol; Estrogen Therapy; Female Sexual Function Index; Female Sexual Dysfunction; Menopause; Vaginal Atrophy

INTRODUCTION

Vulvar and vaginal atrophy (VVA) is a chronic, progressive condition that affects up to 69% of postmenopausal women.[1] Considered a symptom of genitourinary syndrome of menopause,[2] VVA is characterized by the thinning, drying, and loss of elasticity of the vaginal epithelium[3] and clinically manifests as

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symptoms of vaginal dryness, irritation, dysuria, and pain (dyspareunia) or bleeding with sexual activity.[4]

VVA has a negative impact on women's quality of life and has been associated with female sexual dysfunction (FSD). The Real Women's Views of Treatment Options for Menopausal Vaginal Changes (REVIVE) study reported that VVA symptoms interfered with enjoyment of sex in 59% of respondents and 12% of women without a partner reported they were not seeking a sexual partner because of their VVA symptoms.[5] Women respondents in the Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) survey attributed loss of intimacy (58%) and libido (64%) to vaginal dryness.[6] The Menopause Epidemiology study found that VVA was almost four times more likely in women with FSD than in women without FSD.[7]

TX-004HR (TherapeuticsMD Inc, Boca Raton, FL, USA) is an investigational, applicator-free, vaginal-mucosal adhesive, soft gel capsule containing low-dose solubilized 17β-estradiol[8] designed to provide relief from postmenopausal symptoms of VVA, including dyspareunia and vaginal dryness, with negligible to very low systemic absorption. The 12-week, randomized, double-blinded, phase 3 REJOICE trial recently demonstrated that 4-, 10-, and 25-μg doses of TX-004HR were efficacious in treating VVA due to menopause. Specifically, TX-004HR significantly improved the percentage of superficial and parabasal cells and vaginal pH,[8] with negligible to very low absorption of estradiol (average levels did not increase with 4- and 10-μg doses and remained within the normal postmenopausal range $\leq$ 30 pg/mL with the 25-μg dose).[9] Importantly, all three doses significantly improved postmenopausal symptoms of VVA, including dyspareunia, vaginal dryness, and vaginal itching and irritation compared with placebo. Significant improvements in vaginal physiology and dyspareunia were noted as early as 2 weeks and were maintained over the 12-week study period.[8] Based on the previously established association between postmenopausal VVA and sexual function,[5–7] TX-004HR also is expected to have a beneficial effect on sexual function.

AIM

The aim of this study was to evaluate the effects of 12-week treatment with TX-004HR (at doses of 4, 10, or 25 μg) or placebo on FSD, as assessed using the Female Sexual Function Index (FSFI), in postmenopausal women with VVA and the most bothersome symptom of moderate to severe dyspareunia.

METHODS

Study Design

The REJOICE study was a 12-week, multicenter, randomized, double-blinded, parallel-group trial comparing the safety and efficacy of 4-, 10-, and 25-μg doses of TX-004HR with placebo in postmenopausal women diagnosed with VVA. Complete details on the REJOICE study design have been previously reported.[8] Briefly, study participants were randomized 1:1:1:1 to TX-00HR 4, 10, or 25 μg or placebo.[8] TX-004HR is a small, tear-shaped, light pink soft gel capsule containing three different doses of 17β-estradiol (4, 10, or 25 μg). To allow for a double-blinded study design, the TX-004HR and placebo capsules were similar in appearance and, with the exception of the 17β-estradiol, were formulated using the same excipients, including Miglyol 812 (IOI Oleo GmbH, Hamburg, Germany), a fractionated coconut oil (medium-chain triglycerides NF).

Clinical evaluation was performed during the washout period (6–14 weeks before the start of the study), screening period (6 weeks), randomization at baseline, active treatment period (weeks 2, 6, and 8), end of treatment or early termination (12 weeks), and post-study follow-up at week 14.[8] Women self-administered one capsule daily, intravaginally for 2 weeks, followed by biweekly dosing (3–4 days apart) for 10 weeks.[8] Efficacy assessment included changes from baseline to week 12 in the co-primary end points of the percentage of superficial cells, percentage of parabasal cells, vaginal pH, and patient-reported most bothersome symptom of moderate to severe dyspareunia.[8] Additional secondary end points included change from baseline in the severity of vaginal dryness and vulvar and/or vaginal itching or irritation and in the visual evaluation of the vaginal mucosa. FSD also was assessed as a secondary end point at 12 weeks using the FSFI.

The REJOICE trial was designed, conducted, and monitored in accordance with the sponsor's procedure, Good Clinical Practice guidelines, and the principles specified in the Declaration of Helsinki. The study protocol was approved by the institutional review board at all participating centers. Written informed consent was obtained for all study participants.

Study Population

The inclusion and exclusion criteria for the REJOICE study have been previously reported.[8] Postmenopausal women (age 40–75 years; body mass index $\leq$ 38 kg/m^2) with no more than 5% superficial cells on a vaginal cytological smear, vaginal pH higher than 5.0, and the most bothersome symptom of moderate to severe dyspareunia due to menopause were eligible to participate in the trial. In addition, women had to be sexually active (with vaginal penetration) and anticipate sexual activity during the trial period. Postmenopausal women with an intact uterus were required to have an acceptable result from an endometrial biopsy examination conducted at screening.

Women were not permitted to take any oral products containing estrogen, progestin, androgen, or selective estrogen receptor modulators within 8 weeks; transdermal hormones within 4 weeks; vaginal hormones (rings, creams, gels) within 4 weeks; intrauterine progestins within 8 weeks; progestin implants or injectables or estrogen pellets or injectables within 6 months; vaginal lubricants or moisturizers within 7 days before vaginal pH assessment during screening; investigational drugs within 60 days; or an intrauterine device within 12 weeks before screening.

Women with a history of or active clinically important medical diseases (ie, hypersensitivity to estrogens, endometrial hyperplasia, undiagnosed vaginal bleeding, myocardial infarction, or ischemic heart disease) that could potentially confound the study or be detrimental to their well-being were excluded. Women were ineligible to participate in the study if they had a history of estrogen-dependent neoplasia, breast cancer, melanoma, or any gynecologic cancer at any time; a recent history of known alcohol or drug abuse; a current history of heavy smoking (>15 cigarettes/d) or use of e-cigarettes; and a history of sexual abuse or spousal abuse that (in the opinion of the investigator) could interfere with their ability to assess vaginal pain with sexual activity.

Concomitant medications (except for investigational drugs; estrogen, progestin, androgen, or selective estrogen receptor modulators containing medications other than TX-004HR; and prescription and non-prescription medications or remedies for VVA, including vaginal lubricants and moisturizers) were permitted and recorded in diaries during the study period.

MAIN OUTCOME MEASURES

The FSFI is a brief, valid, reliable, multidimensional, self-report instrument for assessing sexual function during the past 4 weeks.[10] The FSFI consists of 19 questions categorized into six domains of sexual function (desire, arousal, lubrication, orgasm, satisfaction, and pain).[10] The FSFI questionnaire was administered to all study participants, except for those participating in the pharmacokinetic sub-study, at baseline and at week 12. Changes in total and individual domain FSFI scores from baseline to week 12 were recorded as a secondary end point of the REJOICE trial.

Scores for each FSFI domain were calculated by adding the scores for the individual domain questions and multiplying by the domain factor (0.6 for desire, 0.3 for arousal and lubrication, and 0.4 for orgasm, satisfaction, and pain). Each FSFI domain is graded using a scale of 0 to 6, with the exception of the desire domain, which is graded on a scale of 1.2 to 6. The total FSFI score is defined as the sum of the individual domain scores and ranges from a minimum score of 2 to a maximum score of 36 points. Sexual dysfunction was defined as a total FSFI score no higher than 26.55 of a maximum possible score of 36.[11]

Statistical Analyses

FSFI analyses were conducted for the modified intent-to-treat population, which consisted of subjects who received treatment to which they were randomized, had baseline values for all four co-primary end points, and at least one post-baseline value for any of the four co-primary end points no more than 7 days after the last dose. Changes from baseline in the total and individual domain FSFI scores were summarized descriptively for each treatment group. Analysis of covariance models were used to compare changes in total and individual domain FSFI scores from baseline to week 12 for each TX-004HR dose vs placebo, with baseline as the covariate.

RESULTS

Participant Disposition and Baseline Characteristics

In total, 764 women were eligible to participate in the REJOICE study, of which 704 (92%) completed the study. The FSFI questionnaire was administered to 692 of the 764 post-menopausal women participating in the REJOICE trial. Women were randomized to TX-004HR 4 μg (n = 173), 10 μg (n = 172), 25 μg (n = 172), or placebo (n = 175).

Demographics and baseline characteristics of the women who completed the FSFI were comparable among the four treatment groups (Tables 1 and 2). Most women were white with mean age of 59 years and a mean body mass index of 27 kg/m^2. The mean total FSFI score was 14.8 at baseline.

Sexual Function

Numerical improvements from baseline to week 12 in total and individual domain FSFI scores were observed for all treatment groups, including placebo (Table 2). Compared with placebo, the improvement in total FSFI score from baseline to 12 weeks was significantly greater with TX-004HR 10- and 25-μg doses (Figure 1).

Baseline scores for FSFI domains of lubrication and pain significantly improved after 12-week treatment with TX-004HR 10 and 25 μg compared with placebo (Figure 2). Statistically significant improvements in FSFI domains of arousal and satisfaction also were seen with TX-004HR 25 μg vs placebo. No statistically significant differences between TX-004HR 4 μg and

Table 1. Demographics and baseline characteristics of Female Sexual Function Index study group

	TX-004HR 4 μg (n = 173)	TX-004HR 10 μg (n = 172)	TX-004HR 25 μg (n = 172)	Placebo (n = 175)
Age (y), mean ± SD	60.0 ± 5.73	58.5 ± 6.22	58.8 ± 6.27	59.3 ± 6.09
Race, n (%)				
White	149 (86.1)	150 (87.2)	149 (86.6)	146 (83.4)
Black or African American	20 (11.6)	20 (11.6)	22 (12.8)	23 (13.1)
Asian	3 (1.7)	2 (1.2)	1 (0.6)	1 (0.6)
BMI (kg/m^2), mean ± SD	26.3 ± 4.77	26.7 ± 4.69	26.5 ± 4.70	26.6 ± 4.52

BMI = body mass index.

Table 2. FSFI scores at baseline and week 12

FSFI score	TX-004HR 4 μg (n = 173)	TX-004HR 10 μg (n = 172)	TX-004HR 25 μg (n = 172)	Placebo (n = 175)
Total				
Baseline, n	173	170	172	174
Mean ± SD	14.8 ± 6.1	15.8 ± 6.2	14.2 ± 6.2	14.4 ± 6.6
Range	2–28.2	2–32.2	2–29.1	2–33.8
Week 12, n	153	154	156	159
Mean ± SD	22.6 ± 8.4	24.8 ± 7.6	24.8 ± 7.6	22 ± 8.5
Range	2–36	2.3–35.4	3.2–36	2–35.6
Arousal				
Baseline, n	173	170	172	175
Mean ± SD	2.8 ± 1.4	2.9 ± 1.4	2.7 ± 1.5	2.7 ± 1.4
Range	0–5.7	0–6	0–6	0–6
Week 12, n	154	154	157	159
Mean ± SD	3.6 ± 1.6	4.1 ± 1.5	4.1 ± 1.4	3.6 ± 1.5
Range	0–6	0–6	0–6	0–6
Desire				
Baseline, n	173	170	172	175
Mean ± SD	2.6 ± 1.0	2.7 ± 1.2	2.6 ± 1.1	2.7 ± 1.1
Range	1.2–6	1.2–6	1.2–6	1.2–6
Week 12, n	154	154	157	159
Mean ± SD	3.3 ± 1.1	3.5 ± 1.1	3.5 ± 1.1	3.3 ± 1.2
Range	1.2–6	1.2–6	1.2–6	1.2–6
Lubrication				
Baseline, n	173	170	172	175
Mean ± SD	2.1 ± 1.2	2.2 ± 1.2	2.0 ± 1.2	2.0 ± 1.3
Range	0–6	0–5.7	0–5.1	0–5.4
Week 12, n	153	154	156	159
Mean ± SD	3.9 ± 1.8	4.4 ± 1.6	4.3 ± 1.7	3.6 ± 1.8
Range	0–6	0–6	0–6	0–6
Orgasm				
Baseline, n	173	170	172	175
Mean ± SD	2.7 ± 1.8	2.9 ± 1.7	2.4 ± 1.7	2.4 ± 1.7
Range	0–6	0–6	0–6	0–6
Week 12, n	153	154	156	159
Mean ± SD	3.8 ± 1.9	4.1 ± 1.8	4.1 ± 1.7	3.7 ± 2.0
Range	0–6	0–6	0–6	0–6
Pain				
Baseline, n	173	170	172	175
Mean ± SD	1.6 ± 1.1	1.8 ± 1.2	1.7 ± 1.2	1.7 ± 1.2
Range	0–4.4	0–5.6	0–5.6	0–5.6
Week 12, n	154	154	156	159
Mean ± SD	3.8 ± 2.0	4.3 ± 1.9	4.2 ± 2.0	3.6 ± 1.9
Range	0–6	0–6	0–6	0–6
Satisfaction				
Baseline, n	173	170	172	174
Mean ± SD	2.9 ± 1.4	3.2 ± 1.4	2.9 ± 1.4	2.9 ± 1.5
Range	0.8–6	0.8–6	0.8–6	0.8–6
Week 12, n	154	154	157	159
Mean ± SD	4.2 ± 1.5	4.4 ± 1.4	4.6 ± 1.4	4.1 ± 1.5
Range	0.8–6	0.8–6	0.8–6	0.8–6

FSFI = Female Sexual Function Index.

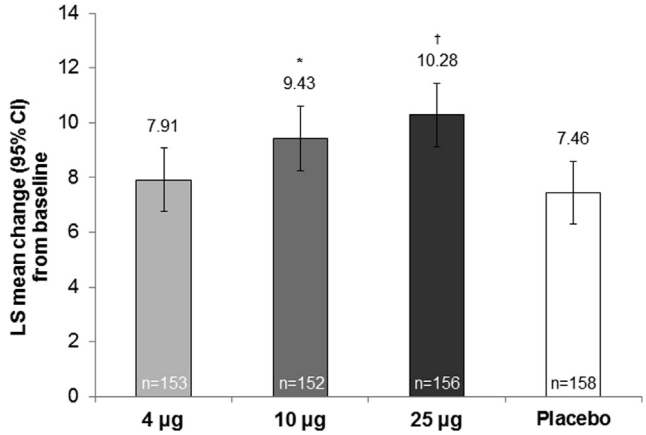

Figure 1. Mean change from baseline to week 12 in total Female Sexual Function Index[10] score. *$P < .05$; †$P = .0019$ vs placebo. LS = least squares.

placebo were observed. All three TX-004HR doses were comparable to placebo in their effect on the FSFI domains of desire and orgasm (Figure 2).

DISCUSSION

In this analysis of the REJOICE trial, TX-004HR improved sexual function in postmenopausal women with moderate to severe VVA and dyspareunia. After 12 weeks, all three TX-004HR doses increased the average baseline total FSFI score (least squares [LS] mean) by a range of 7.91 to 10.28 points, with TX-004HR 10 and 25 μg having statistically significant improvements vs placebo (LS mean change = 7.46). Compared with placebo, TX-004HR 25 μg significantly improved baseline scores for FSFI domains of pain, lubrication, arousal, and satisfaction, and TX-004HR 10 μg improved FSFI pain and lubrication domain scores.

These results extend the observations of the primary data from the REJOICE trial, in which all doses of TX-004HR improved vaginal physiology and dyspareunia as early as 2 weeks after initiating TX-004HR treatment.[8] In addition, improvements in vaginal dryness with TX-004HR were initially seen as soon as week 2 with 10- and 25-μg doses and at week 6 with 4 μg. All three TX-004HR doses were well tolerated, with no clinically significant differences in adverse events compared with the placebo group. The most commonly reported treatment emergent adverse events were headache, vaginal discharge, nasopharyngitis, and vulvovaginal pruritus, with the incidence for each being numerically lower with TX-004HR than with placebo. Study discontinuation owing to adverse events also was low (1.8% of women). A complete description of the TX-004HR safety data from the REJOICE study has been reported.[8] Negligible to very low systemic absorption of estradiol was seen with all doses of TX-004HR, resulting in systemic estradiol levels within the postmenopausal range.[9]

Of the six FSFI domains, TX-004HR had the greatest effect on pain (LS mean change from baseline to week 12 = 2.17−2.55; Figure 2B) followed by lubrication (LS mean change from baseline to week 12 = 1.83−2.30; Figure 2C). This is consistent with the clinically significant decrease in the severity of dyspareunia with TX-004HR (decreased by 55%−65%), in addition to improvements in vaginal dryness (decreased by 54%−63%) and vulvar and/or vaginal irritation or itching (decreased by 67%) reported previously.[8]

Although a head-to-head comparison was not performed, the magnitude of change in total and individual domain FSFI scores with all three TX-004HR doses was comparable to those reported for ospemifene, which was evaluated in postmenopausal women with VVA.[12] Women participating in the two studies were considered to have sexual dysfunction as noted by total FSFI scores of 14.2 to 15.8 in this study and 19.8 in the ospemifene study.[12] After 12 weeks, the improvement in total FSFI score with TX-004HR 4 μg (LS mean change = 7.91), 10 μg (LS mean change = 9.43), and 25 μg (LS mean change = 10.28) was numerically greater than that reported for ospemifene (LS mean change = 7.37 for dyspareunia stratum).[12]

Notably, the two studies differed in the effect of placebo, which was relatively greater in this study than that reported for ospemifene.[12] This is likely due to differences in allowed lubricant use between the studies. Although lubricants were not permitted in this study, the formulation for the placebo and TX-004HR vaginal capsules contained Miglyol, a fractionated coconut oil that might have lubricating properties. Thus, continuous exposure to Miglyol with placebo could have contributed to the large placebo response seen in this study. In contrast, lubricant use was allowed as needed in the ospemifene study[12] rather than on a continual basis, so the placebo response would not be expected to be as great as that reported in our study.

The significant improvement in total FSFI and FSFI pain and lubrication domain scores with higher TX-004HR doses, despite the large placebo response, suggests TX-004HR has an added positive effect on sexual function, a likely result of the improvement in vaginal physiology and dyspareunia. Because many factors, such as sexual desire, arousal, orgasm, woman's confidence, and relationship status, associated with overall sexual health are highly comorbid, continuous use of TX-004HR would be expected to improve sexual dysfunction in postmenopausal women with VVA. Although this would be consistent with the reported association between postmenopausal VVA and sexual dysfunction,[5–7] longer-term clinical studies would be needed to confirm these initial hypotheses.

The generalizability of the findings might be limited by the women being primarily white with a high body mass index (26 kg/m^2). Another limitation of this analysis is that the effect of TX-004HR on sexual function with the FSFI was evaluated as a secondary end point of the REJOICE study. Despite being widely used, the FSFI has not been validated in a population of postmenopausal women with VVA, but rather in a mixed sample population of women with female sexual arousal disorder,

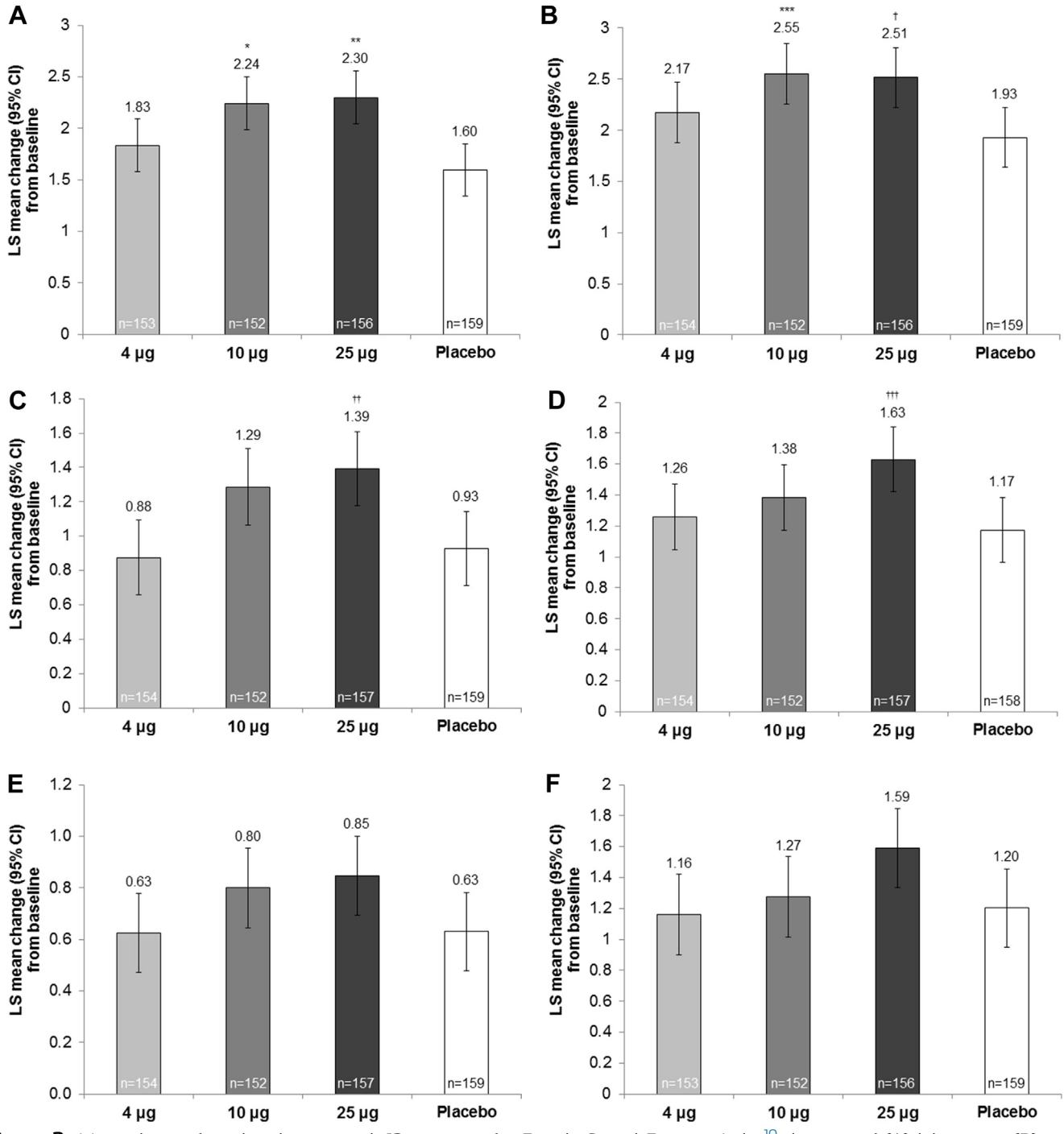

Figure 2. Mean change from baseline to week 12 in scores for Female Sexual Function Index[10] domains of (A) lubrication, (B) pain, (C) arousal, (D) satisfaction, (E) desire, and (F) orgasm. *$P = .0013$; **$P = .0003$; ***$P < .01$; †$P = .015$; ††$P = .0085$; †††$P = .0073$ vs placebo. FSFI = Female Sexual Function Index; LS = least squares.

hypoactive sexual desire disorder, female sexual orgasm disorder, dyspareunia or vaginismus, and multiple sexual dysfunctions. Furthermore, the REJOICE study was designed according to the U.S. Food and Drug Administration's guidance for evaluating estrogen-based treatments for VVA[13] rather than FSD. However, as previously stated, the improvements in total and individual domain scores of the FSFI were comparable to those seen with ospemifene, suggesting that TX-004HR could improve sexual function in postmenopausal women with VVA. No FSFI data have been reported for any of the low-dose vaginal estrogens approved in the United States.

CONCLUSION

TX-004HR dose-dependently improved sexual function in postmenopausal women with VVA participating in the phase 3,

randomized, double-blinded, placebo-controlled REJOICE trial as measured by the FSFI. All three TX-004HR doses and placebo increased total FSFI and individual domain FSFI scores after 12 weeks, with 25 μg having the greatest effect compared with placebo. In addition, the REJOICE trial reported significant improvement in the co-primary end points (percentage of parabasal and superficial cells and vaginal pH) for postmenopausal VVA and reduced the severity of dyspareunia after 12 weeks of TX-004HR treatment, with significant effects seen as early as 2 weeks of treatment. The present FSFI data coupled with improvement in vaginal physiology suggest that TX-004HR could be a promising treatment option for VVA, with a potential added benefit of improving FSD in postmenopausal women.

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Conflicts of Interest: Dr Kingsberg has served as a consultant for TherapeuticsMD Inc, Novo Nordisk Inc, Pfizer Inc, Palatin, Emotional Brain, Sprout Pharmaceuticals Inc, Valeant Pharmaceuticals Inc, Sermonix Pharmaceuticals Inc, Nuelle Inc, Apricus Inc, and Materna. Dr Derogatis is a clinical trials investigator and a member of the scientific advisory board for Palatin Pharmaceuticals, S1 Biopharam, Emotional Brain, Acerus, and Endoceutics and has seved as an investigator for AbbVie Inc and TherapeuticsMD. Dr Simon has served (within the past year) or is currently serving as a consultant to or on the advisory boards of AbbVie Inc, AMAG Pharmaceuticals Inc, Amgen Inc, Apotex Inc, Ascend Therapeutics, JDS Therapeutics LLC, Merck & Co Inc, Noven Pharmaceuticals Inc, Novo Nordisk, Nuelle Inc, Perrigo Company PLC, Radius Health Inc, Regeneron Pharmaceuticals Inc, Roivant Sciences Inc, Sanofi SA, Sermonix Pharmaceuticals Inc, Shionogi Inc, Sprout Pharmaceuticals, Symbiotec Pharmalab, and TherapeuticsMD; has served (within the past year) or is currently serving on the speaker's bureaus of Amgen Inc, Eisai Inc, Merck, Noven Pharmaceuticals Inc, Novo Nordisk, and Shionogi Inc; in the past year has received or is currently receiving grant or research support from AbbVie Inc, Actavis PLC, Agile Therapeutics, Bayer Healthcare LLC, New England Research Institute Inc, Novo Nordisk, Palatin Technologies, Symbio Research Inc, TherapeuticsMD; and is a stockholder (direct purchase) of Sermonix Pharmaceuticals. Dr Constantine consults to pharmaceutical companies, including but not limited to TherapeuticsMD. Dr Bernick is a board member and an employee of TherapeuticsMD with stock and stock options. Dr Graham, Ms. Gasper, and Dr Mirkin are employees of TherapeuticsMD with stock and stock options.

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