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Efficacy and safety of ospemifene in postmenopausal women with moderate-to-severe vaginal dryness: a phase 3, randomized, double-blind, placebo-controlled, multicenter trial

David F. Archer, MD,[1] Steven R. Goldstein, MD,[2] James A. Simon, MD,[3] Arthur S. Waldbaum, MD,[4] Steven A. Sussman, MD,[5] Corrado Altomare, MD,[6] Julie Zhu, MD,[6] Yuki Yoshida,[6] Sam Schaffer, MD,[7] and Graziella Soulban, PhD[7]

Abstract

Objective: To evaluate the safety and efficacy of ospemifene for the treatment of moderate to severe vaginal dryness in postmenopausal women with vulvovaginal atrophy (VVA).

Methods: This 12-week, multicenter, double-blind phase 3 study randomized postmenopausal women (aged 40-80 years) with VVA and moderate to severe vaginal dryness as their most bothersome symptom to daily oral ospemifene 60 mg or placebo. Coprimary efficacy endpoints included changes from baseline to week 12 in percentages of vaginal parabasal and superficial cells, vaginal pH, and vaginal dryness severity with ospemifene versus placebo; other secondary endpoints were evaluated (weeks 4, 8, and 12). Safety was assessed by treatment-emergent adverse events (TEAEs) and endometrial biopsies.

Results: Women (n = 631; ospemifene [n = 316], placebo [n = 315]) had a mean age of 59.8 years, a mean body mass index of 27.2 kg/m^2, and most were white. Ospemifene significantly improved ($P < 0.0001$) the percentages of parabasal and superficial cells, vaginal pH, and severity of vaginal dryness severity compared with placebo at week 12; significant between-group differences were noted by week 4. Secondary endpoints of dyspareunia ($P < 0.001$), maturation value ($P < 0.0001$), and the Female Sexual Function Index ($P < 0.05$) also significantly improved with ospemifene versus placebo at week 12. Significantly more women responded (31.5% vs 6.0%; $P < 0.0001$) or were satisfied (49.2% vs 33.8%; $P = 0.0007$) with ospemifene versus placebo at week 12. No unexpected TEAEs, treatment-related serious TEAEs, thrombotic events, or endometrial hyperplasia or carcinoma were observed.

Conclusions: Ospemifene was effective and well tolerated for the treatment of moderate-to-severe vaginal dryness in postmenopausal women with VVA.

Key Words: Dyspareunia – Menopause – Ospemifene – Selective estrogen receptor modulator – Vaginal dryness.

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From the [1]Eastern Virginia Medical School, Norfolk, VA; [2]New York University School of Medicine, New York, NY; [3]IntimMedicine Specialists, Washington, DC; [4]Downtown Women's Healthcare, Denver, CO; [5]Lawrence OB/GYN Associates, Lawrenceville, NJ; [6]Shionogi Inc, Florham Park, NJ; and [7]Duchesnay Inc, Quebec, Canada.

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Address correspondence to: David F. Archer, MD, Eastern Virginia Medical School, 601 Colley Ave, Norfolk, VA 23507-1912. E-mail: archerdf@evms.edu

Vulvovaginal atrophy (VVA) is a common, chronic, and bothersome condition that results from declining estrogen levels during and after the menopausal transition,[1,2] and is part of the genitourinary syndrome of menopause.[3] Physiologic changes of VVA include the thinning and drying of the vaginal epithelium, which can result in symptoms such as vaginal dryness, itching, burning, and dyspareunia, all of which can have a substantial impact on quality of life and sexual health.[4-7] Of the 40% to 60% of women in the United States and international surveys who reported VVA symptoms, approximately 50% to 60% rated their symptoms as moderate to severe.[5,6,8,9] The most commonly reported symptom in surveys was vaginal dryness, reported by up to 85% of women with VVA.[5-8,10] The recent cross-sectional, observational, multicenter Atrophy of the vaGina in womAn in posT-menopause in ItAly study ($N > 900$) also found that vaginal dryness was the most frequently reported VVA symptom.[11] Despite the significant detrimental impact of VVA symptoms, few women seek medical attention.[5,7,9] One reason women cite for not discussing VVA symptoms with a healthcare professional is a lack of awareness about available treatment options.[6]

Current treatment options for VVA include nonhormone, over-the-counter lubricants and moisturizers, vaginal estrogen therapies (creams, tablets, rings), vaginal dehydroepiandrosterone treatment, and systemic hormone therapy.[1,2] These treatment options, however, have limitations. Concerns about incorrect dose administration, leakage, and mess of vaginal formulations[12] may affect the use of creams, moisturizers, and lubricants, and some women may prefer oral treatments over vaginal therapies due to ease of use.[7] These challenges may be reflected in the low rates of satisfaction with vaginal prescription therapies, lubricants, and moisturizers.[6,7,10] A recent survey found that women who were most satisfied with their VVA treatment were those who took an oral selective estrogen receptor modulator (SERM).[6] In addition, concerns regarding the risks of long-term use of systemic hormone therapy may limit its use in the management of VVA, particularly in the absence of other menopausal symptoms.[1,2] Moreover, many of the systemic and local therapies prescribed for VVA have not been formally evaluated for vaginal dryness.

Ospemifene is an oral SERM, also known as an estrogen receptor agonist/antagonist, that has tissue-specific estrogenic or antiestrogenic effects, acting selectively as an estrogen receptor agonist on the vulva and vagina.[13-15] It is currently approved for the treatment of moderate to severe dyspareunia due to menopausal VVA in the United States,[16] and for the treatment of moderate to severe symptomatic VVA in postmenopausal women who are not candidates for local vaginal estrogen therapy in the European Union.[17] As an estrogen receptor agonist on the vulva and vagina, ospemifene has been shown to have clinically and statistically significant improvements on vaginal epithelial maturation and dyspareunia in two phase 3 clinical trials, and on vaginal dryness in one phase 3 study.[13-15] Other trials also confirmed the safety of ospemifene for up to 1 year, finding no significant estrogenic or clinically relevant adverse effects on the endometrium or the breast.[18-20]

This phase 3 confirmatory study was conducted to evaluate the efficacy and safety of daily, oral ospemifene 60 mg for the treatment of moderate to severe vaginal dryness as the most bothersome symptom (MBS) of VVA due to menopause.

METHODS

Study design

This 12-week, double-blind, randomized, parallel-group, placebo-controlled, phase 3 clinical trial was conducted at 68 study centers in the United States between January 2016 and July 2017 (NCT02638337). After a screening period of up to 4 weeks, eligible participants were randomized 1:1 to daily ospemifene 60 mg (Osphena, Shionogi Inc, Florham Park, NJ) or matching placebo for up to 12 weeks based on a computer-generated randomization schedule prepared by an independent statistician before study start. Randomization was stratified by moderate or severe vaginal dryness and the presence or absence of a uterus (limited to 60% of participants without a uterus in each group), so that similar proportions of women in each category were in each treatment group. All study staff and participants were blinded throughout the study; ospemifene 60 mg and placebo tablets were identical in appearance and packaging. Women were instructed to take study drug once daily with food at approximately the same time each day. Study participants were provided with a nonhormone, water-based lubricant (K-Y Jelly, Reckitt Benckiser, Slough, England) to use as needed during sexual activity. Lubricant use was recorded by participants in a daily diary. Two weeks after the last dose of study drug, women had a follow-up visit/telephone contact to assess adverse events (AEs) and use of concomitant therapy.

The protocol was reviewed and approved by a central institutional review board, and the study was conducted in accordance with the Declaration of Helsinki and current Good Clinical Practice guidelines. Written informed consent was provided by all participants before initiating the study.

Study population

Participants were 40 to 80 years of age and postmenopausal (defined as $\geq$12 prior months since their last spontaneous menstrual bleeding episode in women aged $\geq$45 years, $\geq$6 weeks since bilateral oophorectomy, or having a serum follicle-stimulating hormone level >40 IU/L for hysterectomized women with intact ovaries or women aged $\geq$45 years with an unknown date of their last spontaneous menstrual bleed). Women rated their MBS of VVA (recommended by the Food and Drug Administration [FDA] for a symptom indication[21]) at baseline on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe) using a validated, patient self-assessment of VVA questionnaire. Women who reported moderate or severe vaginal dryness as their MBS with 5% or lesser superficial cells on their vaginal wall smear and a vaginal pH more than 5.0 were eligible to participate.

Women were excluded if they had any of the following at screening: a double-layer endometrial thickness of 4 mm or higher on a centrally read transvaginal ultrasound, pathological finding on Papanicolaou test or endometrial biopsy, or any clinically significant abnormality on physical or gynecological examinations other than VVA. Women were also excluded if they had a body mass index of 38 kg/m^2 or higer, uncontrolled hypertension (blood pressure $\geq$140/$\geq$90) or clinically relevant abnormality in safety laboratory tests or electrocardiograms; were suspected of having or had a malignancy within 10 years; had a history of thromboembolic or coagulation disorders, cerebrovascular accident, cardiac ischemic disorders, or hepatic impairment; or had moderate or severe renal impairment. In addition, women who consumed more than 14 alcoholic beverages per week; used any vaginal, transdermal, systemic, intrauterine, implantable, or injectable hormone therapy without a sufficient washout period; used any SERM within 60 days; or were currently using systemic fluconazole, rifampicin, rifabutin, carbamazepine, phenytoin, or St John wort were excluded. During the study, women could not use any of the above medications or any vaginal lubricant or moisturizer not provided by the sponsor.

Study outcomes

The four co-primary efficacy endpoints were changes from baseline to week 12 in the percentages of parabasal cells and superficial cells, vaginal pH, and severity of the self-reported MBS of vaginal dryness. Vaginal smears were taken from the middle third of the lateral vaginal wall and proportions of parabasal and superficial cells were determined at a central laboratory. Vaginal pH was measured by pressing a pH indicator strip against the vaginal wall. Severity of the MBS was assessed with the same patient self-assessment of VVA questionnaire used at baseline.

Among the secondary endpoints were changes in percentages of parabasal and superficial cells, vaginal pH, and severity of vaginal dryness at weeks 4 and 8. Other secondary endpoints collected at weeks 4, 8, and 12 were changes from baseline in VVA symptoms other than vaginal dryness such as vaginal and/or vulvar irritation or itching, dyspareunia, and vaginal bleeding with sexual intercourse; change from baseline in maturation value (MV; $MV = [S \times 1] + [I \times 0.5] + [P \times 0]$, where S = percentage of superficial cells, I = percentage of intermediate cells, P = percentage of parabasal cells); and the proportion of responders (defined as those with improvements from baseline in the MV of $\geq$10 points, in vaginal pH of $\geq$0.5, and in the MBS of vaginal dryness of $\geq$1 point). Changes from baseline in the Female Sexual Function Index (FSFI) scores were also secondary endpoint collected at weeks 4, 8, and 12. The FSFI is a brief, validated, self-report instrument for assessing sexual function during the past 4 weeks, and consists of 19 questions categorized into 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and pain.[22] Overall satisfaction at each week of the study (very satisfied, moderately satisfied, equally satisfied/dissatisfied, moderately dissatisfied, and very dissatisfied) and frequency of lubricant use and sexual activity (recorded in daily electronic diaries) were also secondary endpoints.

Study participants were asked to report all AEs throughout the study and each study visit. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 18.0), and treatment-emergent AEs (TEAEs) were summarized by treatment group, system organ class, preferred term, causality, and severity. TEAEs were defined as AEs reported after the initial study dose and up to 14 days after the last dose. Safety was also assessed by gynecological examination, breast palpation, cervical Papanicolaou tests, clinical laboratory analyses, electrocardiograms, physical examinations, and vital signs. Central laboratory analyses of a transvaginal ultrasound to assess endometrial thickness and histology from endometrial biopsies were performed on all participants with an intact uterus at baseline and week 12. All endometrial histology samples were reviewed by three independent pathologists who were blinded to treatment and each other's readings. A diagnosis was made with a concurrence of two of the three pathologists' readings; with no agreement among the three, the most severe pathologist's histological reading was used as the diagnosis.

Statistical analyses

A sample size of 600 participants (300 per treatment arm) was calculated to provide 90% or more power for comparison between ospemifene 60 mg and placebo in the 4 coprimary efficacy endpoints with a 2-sided significance level of 0.05. Although all efficacy endpoints were analyzed in the intent-to-treat (ITT) population (defined as randomized participants who received at least 1 dose of study medication according to their randomization assignment), modified ITT (mITT) and per protocol (PP) populations were also analyzed. The mITT population included women of the ITT population who met the inclusion criteria of 5% or less superficial cells, vaginal pH higher than 5.0, and an MBS of vaginal dryness. The PP population included those who completed treatment of 10 weeks more, took 85% or more of study drug, did not have any major protocol violations within 12 weeks, and did not have a vaginal infection or medical condition that would confound the primary efficacy assessment. The safety population included all randomized women who received 1 or more dose of study drug.

A mixed-effects model for repeated measures (MMRMs) approach was used to analyze changes in the percentages of parabasal cells and superficial cells, vaginal pH, and severity of vaginal dryness (as a sensitivity analysis for this endpoint only) between groups at week 12. A generalized estimating equations (GEEs) model was used to fit a marginal proportional odds model to the longitudinal ordered categorical data as the primary analysis for the change in MBS of vaginal dryness. For both models, repeated measurements of the change from baseline at weeks 4, 8, and 12 were the response variables; treatment, week, treatment-by-week interaction, and study center were fixed effects; and baseline value was a covariate. These outcomes as secondary endpoints were

analyzed the same as the primary endpoints (at weeks 4 and 8).

Changes in the severity of VVA symptoms other than vaginal dryness were analyzed the same as changes in vaginal dryness at weeks 4, 8, and 12 using the GEE model. Other secondary endpoints analyzed between groups at weeks 4, 8, and 12 were changes in the FSFI total score and MV analyzed by analysis of covariance with baseline score as a covariate; proportion of responders using Fisher exact test; lubricant use and sexual activity frequencies using Welch *t* test; and proportions of women compared over the different overall satisfaction categories using the Wilcoxon rank-sum test. Summary statistics were generated for quantitative demographics, frequencies and proportions for qualitative demographics, and summary tables for TEAEs.

No last observation carried forward methods were used to impute missing data; all analyses were based on observed results as per MMRM. All statistical tests were performed at the 0.05 significant level using two-sided tests.

RESULTS

Participant disposition and demographics

Of the 2,058 women screened, 631 were enrolled and randomized to ospemifene (n = 316) or placebo (n = 315; Fig. 1). The majority of women who received ospemifene and placebo were included in the ITT population (99.1% vs 99.7%) and completed the 12-week study (89.6% vs 88.6%). The primary reason for study discontinuation was due to participant withdrawal (ospemifene, 4.1%; placebo, 5.1%). Study discontinuation due to AEs was low (ospemifene, 1.9%; placebo, 3.2%).

Demographics and baseline characteristics were similar between treatment groups (Table 1). Mean age was approximately 60 years, mean body mass index was 27.2 kg/m^2, and mean duration of VVA was 8 to 9 years (Table 1). The majority of women were white (85%–87%) and did not have an intact uterus (58%–59%; Table 1). Similar percentages of women who had a prior bilateral oophorectomy or salpingo-oophorectomy were in the ospemifene (8.0%) and placebo (8.9%) groups. Most women in each group did not have hot flushes entering the study (91%–92%) and did not previously take hormone therapy (97%–98%; Table 1). More than half of participants had severe vaginal dryness at baseline (Table 1).

Primary efficacy endpoints

Changes from baseline in each of the 4 coprimary endpoints improved significantly more with ospemifene 60 mg than with placebo in the ITT population. Similar results were observed in the mITT and PP populations (data not shown). Ospemifene compared with placebo significantly decreased the percentage of parabasal cells (least square [LS] mean changes −23.7% vs −1.9%, $P < 0.0001$) and significantly

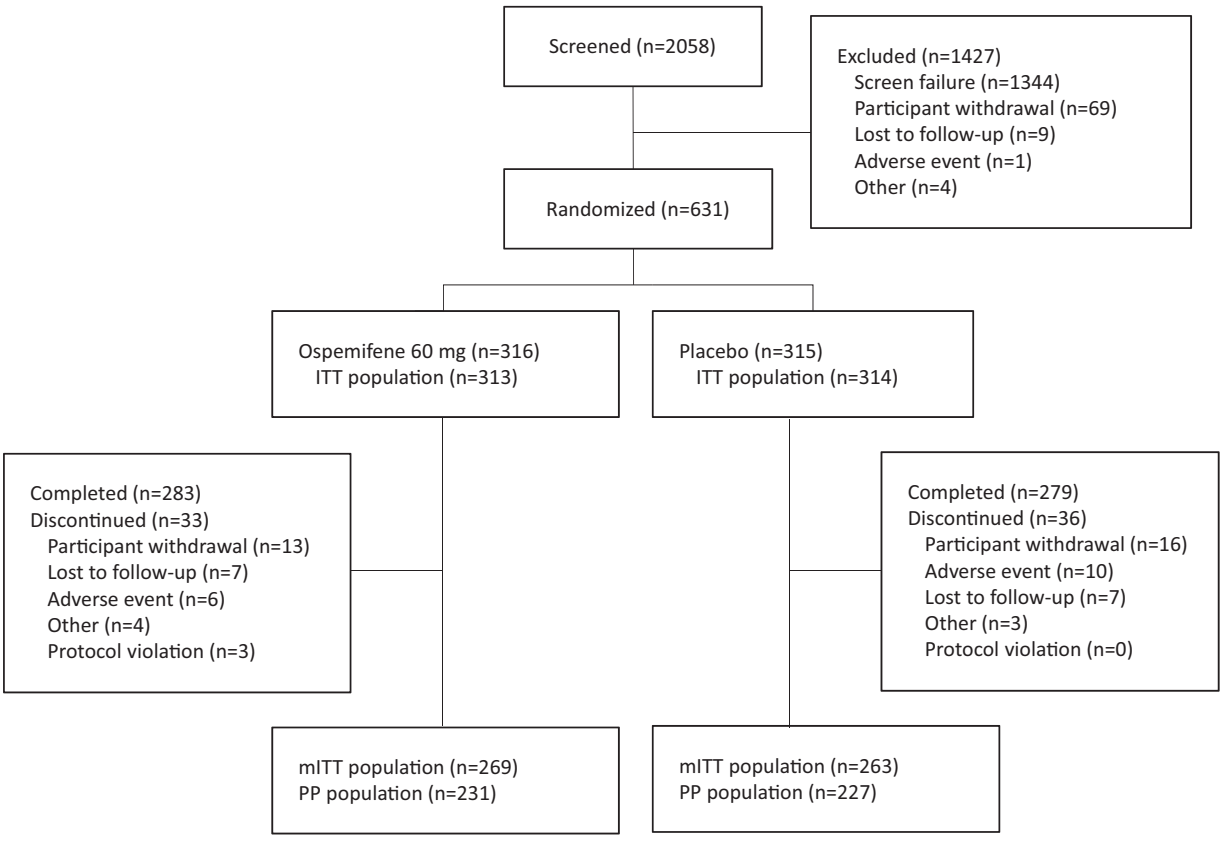

FIG. 1. Participant disposition. ITT, intent-to-treat; mITT, modified intent-to-treat; PP, per protocol.

TABLE 1. *Participant demographics and baseline characteristics in the intent-to-treat population*

	Ospemifene (n = 313)	Placebo (n = 314)
Age, mean ± SD, y	59.7 ± 6.6	59.8 ± 7.2
Race, n (%)		
White	273 (87.2)	266 (84.7)
Black	38 (12.1)	32 (10.2)
American Indian or Alaska Native	0	7 (2.2)
Asian	1 (0.3)	3 (1.0)
Other	1 (0.3)	6 (1.9)
BMI, mean ± SD, kg/m^2	27.3 ± 4.5	27.1 ± 4.8
No uterus, n (%)	185 (59.1)	182 (58.0)
Not currently experiencing hot flushes, n (%)	287 (91.7)	286 (91.1)
No previous hormone therapy, n (%)	305 (97.4)	307 (97.8)
Duration of VVA, mean ± SD, y	8.4 ± 6.9	9.0 ± 7.8
Vaginal parameters, mean ± SD		
Parabasal cells, %[a]	25.8 ± 33.3	28.3 ± 33.1
Superficial cells, %[a]	3.0 ± 7.6	2.8 ± 6.9
Vaginal pH	6.1 ± 0.7	6.1 ± 0.7
Vaginal dryness MBS severity score	2.5 ± 0.5	2.5 ± 0.5
Vaginal dryness severity, n (%)		
Moderate	148 (47.3)	143 (45.5)
Severe	165 (52.7)	171 (54.5)

BMI, body mass index; ITT, intent-to-treat; MBS, most bothersome symptom; SD, standard deviation; VVA, vulvar and vaginal atrophy.
[a]n = 306 and 308 for ospemifene and placebo, respectively.

increased the percentage of superficial cells (7.8% vs 0.6%, $P < 0.0001$) after 12 weeks of treatment (Fig. 2AB). Ospemifene also significantly reduced vaginal pH (Fig. 2C); decreases were −1.01 with ospemifene and −0.29 with placebo ($P < 0.0001$) at week 12. More women in the ospemifene group had improvements of 1, 2, or 3 points in the severity of vaginal dryness MBS than women in the placebo group (Fig. 3). Women who took ospemifene were approximately two times more likely to experience improvement in the MBS vaginal dryness severity score than women who took placebo (odds ratio 2.23, 95% CI, 1.62-3.06 at week 12; see Supplemental Table 1 [http://links.lww.com/MENO/A371], which shows changes from baseline in vaginal dryness). Significant improvements in the mean vaginal dryness score were found with ospemifene versus placebo at weeks 4, 8, and 12 in the ITT population (−1.29 vs −0.91, $P < 0.0001$ at week 12).

Secondary efficacy endpoints

Significant improvements in the percentages of superficial and parabasal cells, vaginal pH, and severity of vaginal dryness with ospemifene versus placebo before week 12 were seen as early as week 4 ($P < 0.0001$ for all comparisons at weeks 4 and 8, except for $P = 0.0005$ for severity of vaginal dryness at week 4).

Ospemifene significantly reduced the severity of dyspareunia compared with placebo at week 4 (−1.24 vs −0.99, $P = 0.0095$) and week 12 (−1.55 vs −1.21, $P = 0.0004$, odds ratio of 1.97; Table 2) for women with moderate to severe symptoms at baseline. The mean changes from baseline in severity of vaginal and/or vulvar irritation or itching and vaginal bleeding with intercourse were similar between groups (Table 2).

Ospemifene significantly increased the MV relative to placebo by week 4 with continued significant differences at weeks 8 and 12 (the difference in LS mean change from baseline between ospemifene and placebo ranged from 13.98 at week 4 to 14.91 at week 12 [$P < 0.0001$]). Similarly, the percentages of responders (women who experienced improvements from baseline of ≥10 points in vaginal maturation, ≥0.5 points in vaginal pH, and ≥1 point in the MBS of vaginal dryness) were significantly greater in the ospemifene group than in the placebo group as early as week 4 (19.2% vs 2.6%) and continued to week 12 (31.5% vs 6.0%; $P < 0.0001$ at all timepoints; Fig. 4).

Women in the ospemifene group reported significantly higher FSFI total scores than women in the placebo group (5.7 vs 4.1, $P = 0.0392$) at week 12 (Table 2; Fig. 5). FSFI scores for all of the domains at week 12 are listed in Table 2. Differences in LS mean changes from baseline for the FSFI lubrication and pain domains with ospemifene versus placebo were significant at week 12 (Table 2), but not at week 4 (data not shown).

Overall satisfaction was significantly greater for women who took ospemifene than for women who took placebo at all weeks from weeks 2 to 12 (see Fig. 6 for week 12). Significantly more women were very satisfied or moderately satisfied with ospemifene than with placebo at week 12 (69.7% vs 53.5%; $P = 0.0007$). The frequency (mean number of days ± SD per week) of lubricant use throughout the study did not change with ospemifene or placebo and was similar between groups (0.8 ± 1.3 vs 0.8 ± 1.2 days per week; $P = 0.9575$) over the 12-week study. Similarly, sexual activity frequency (mean days of intercourse ± SD per week) was not different between the ospemifene and placebo groups (0.9 ± 1.0 vs 0.9 ± 1.1 days per week; $P = 0.8772$).

Safety

TEAEs were reported in 35.3% of women in the ospemifene group and 33.2% in the placebo group (Table 3). The most frequently reported TEAE was hot flush, reported by 6.3% in the ospemifene group and 2.6% in the placebo group (Table 3). Three women (0.9%) in the ospemifene group and one (0.1%) in placebo group discontinued the study due to the hot flush TEAE. Overall, most TEAEs were considered not related to treatment, but more treatment-related AEs were noted for ospemifene versus placebo (Table 3) mostly due to the incidence of treatment-related hot flushes (5.7% vs 2.6%). Vaginal bleeding TEAEs occurred in four (1.3%) women with ospemifene and one (0.3%) woman with placebo; two of these cases in the ospemifene group were considered related to treatment, but were mild, resolved without treatment, and were likely associated with vaginal atrophy. One case of vaginal bleeding in the ospemifene group led to study

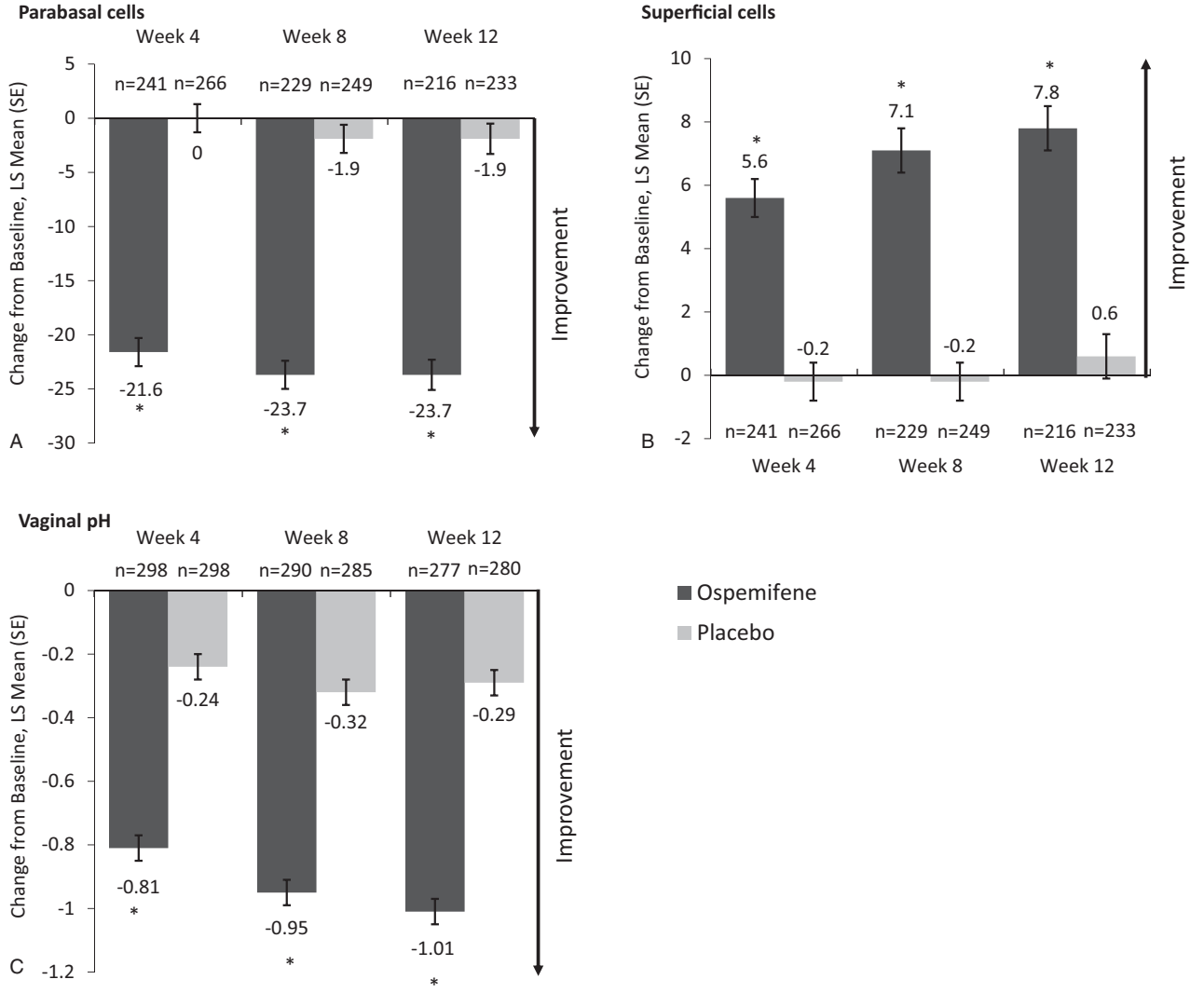

FIG. 2. LS mean changes (±SE) from baseline in (**A**) parabasal cells, (**B**) superficial cells, and (**C**) vaginal pH at weeks 4, 8, and 12 in the ITT population. $^{*}P < 0.0001$ versus placebo. ITT, intent-to-treat; LS, least squares; SE, standard error.

withdrawal. Most TEAEs were considered mild to moderate in nature.

Two breast-related TEAEs were reported with ospemifene; breast enlargement (n = 1) and breast tenderness (n = 1). Serious TEAEs were reported by eight participants during the 12 treatment weeks, five (1.6%) women in the ospemifene group experienced six events and three (1.0%) in the placebo group (Table 3), none of which were considered related to treatment. One acute myocardial infarction occurred in the ospemifene group in a woman with cardiovascular risk factors; and no thromboembolic events occurred in either group. Two serious, unrelated TEAEs occurred in the ospemifene group after week 12. No deaths occurred during the study.

No cases of endometrial hyperplasia or carcinoma were observed. Mean changes in endometrial thickness at week 12 were 0.63 mm with ospemifene and −0.23 mm with placebo (Table 4). Four women (two ospemifene; two placebo) did not have baseline endometrial biopsies. Overall, little change was noted in the distribution of endometrial histology classifications from baseline to week 12 (Table 4). Generally, decreased percentages of atrophy and increased percentages of benign inactive, weakly proliferative and active proliferative endometrium were found with ospemifene, and increased percentages of atrophy with placebo, from baseline to week 12.

DISCUSSION

This randomized, placebo-controlled, phase 3 study confirms the vaginal physiological benefits and shows vaginal dryness improvements with ospemifene in postmenopausal women experiencing moderate to severe vaginal dryness as their MBS of VVA. Ospemifene significantly improved all coprimary efficacy endpoints (percentages of vaginal epithelial cells, vaginal pH, and vaginal dryness severity) versus placebo at 12 weeks. In secondary analyses, improvements in these objective and subjective outcomes with ospemifene

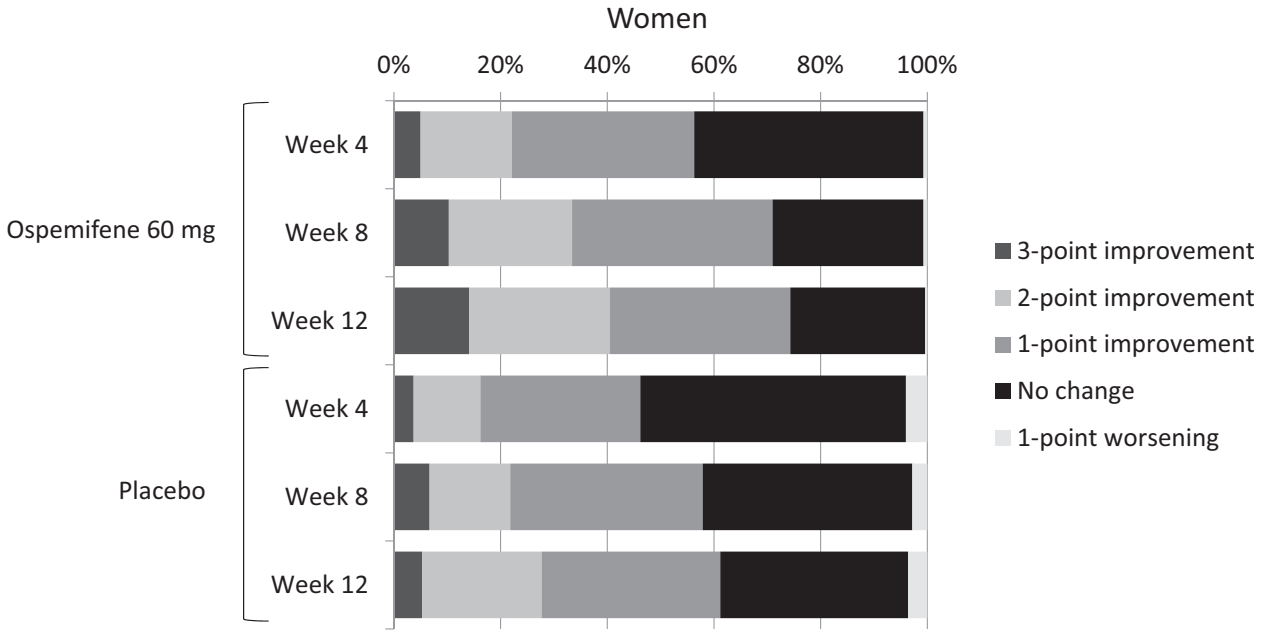

FIG. 3. Changes in points for severity scores of vaginal dryness as the MBS at weeks 4, 8, and 12 in the ITT population (GEE model). GEE, generalized estimating equations; ITT, intent-to-treat; MBS, most bothersome symptom.

were apparent as early as week 4, and statistically significant and clinically meaningful improvements in dyspareunia, the MV, and sexual function as assessed by the FSFI were observed. In addition, the percentage of responders was significantly higher with ospemifene compared with placebo; in fact, by week 12, 5 times as many women taking ospemifene versus those taking placebo responded to treatment. Ospemifene also had a good safety profile and was well tolerated, with no new unanticipated safety issues.

Results reported here are consistent with the findings from previous randomized, double-blind, placebo-controlled phase 3 studies of ospemifene in postmenopausal women with VVA.[13-15] Indeed, in previous studies ospemifene 60 mg daily statistically and clinically significantly improved vaginal

TABLE 2. *Mean changes from baseline in secondary efficacy endpoints at week 12*

Symptoms other than vaginal dryness	Ospemifene (n = 313)	Placebo (n = 314)	Odds ratio (95% CI)	*P*
Dyspareunia severity, mean ± SD				
Baseline	2.5 ± 0.5	2.5 ± 0.5		
Change from baseline	−1.6 ± 1.0	−1.2 ± 1.1	1.97 (1.35, 2.88)	0.0004
Vaginal and/or vulvar irritation and/or itching, mean ± SD				
Baseline	2.3 ± 0.4	2.3 ± 0.4		
Change from baseline	−1.4 ± 1.0	−1.4 ± 1.0	1.03 (0.65, 1.64)	0.8894
Vaginal bleeding during intercourse, mean ± SD				
Baseline	2.2 ± 0.4	2.3 ± 0.5		
Change from baseline	−1.6 ± 0.8	−1.6 ± 1.1	0.86 (0.39, 1.89)	0.7101
Other secondary endpoints	**Ospemifene (n = 313)**	**Placebo (n = 314)**	**Difference of LS mean (95% CI)**	***P***
Maturation value				
Baseline, mean ± SD	38.6 ± 18.0	37.3 ± 18.0		
Change from baseline, LS mean ± SE	16.2 ± 0.9	1.3 ± 0.8	14.9 (12.6, 17.3)	<0.0001
FSFI, total score				
Baseline, mean ± SD	13.1 ± 7.4	13.1 ± 7.3		
Change from baseline, LS mean ± SE	5.7 ± 0.6	4.1 ± 0.5	1.6 (0.08, 3.09)	0.0392
FSFI domains, change from baseline, LS mean ± SE				
Desire	0.56 ± 0.07	0.39 ± 0.06	0.16 (−0.02, 0.34)	0.0752
Arousal	0.64 ± 0.11	0.44 ± 0.11	0.20 (−0.10, 0.49)	0.1867
Lubrication	1.29 ± 0.12	0.89 ± 0.12	0.40 (0.07, 0.73)	0.0161
Orgasm	0.78 ± 0.12	0.63 ± 0.11	0.16 (−0.16, 0.48)	0.3400
Satisfaction	0.78 ± 0.09	0.62 ± 0.09	0.16 (−0.10, 0.41)	0.2195
Pain	1.47 ± 0.12	1.01 ± 0.12	0.45 (0.11, 0.80)	0.0103

CI, confidence interval; FSFI, Female Sexual Function Index; LS, least squares; SD, standard deviation; SE, standard error.

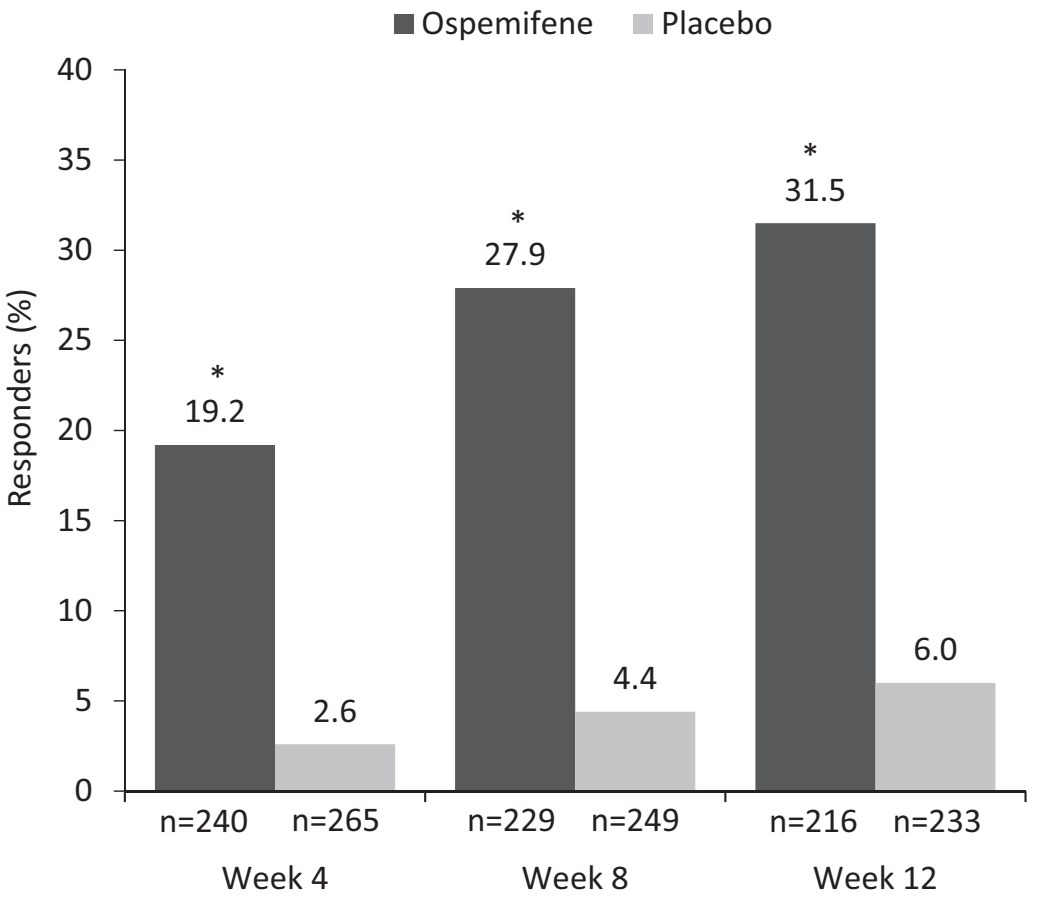

FIG. 4. Proportion of responders with ospemifene and placebo at weeks 4, 8, and 12 (ITT population). $^{*}P < 0.0001$ versus placebo. A responder was a woman who experienced improvements from baseline of 10 points or more in the maturation value, 0.5 points or more in vaginal pH, and 1 point or more in the MBS of vaginal dryness severity. ITT, intent-to-treat; MBS, most bothersome symptom.

physiology including increases in the percentage of superficial cells, decreases in the percentage of parabasal cells, and reductions in vaginal pH.[13-15] This study also confirms the onset of effect on these objective coprimary endpoints as 4 weeks of treatment, also as demonstrated in previous studies.[13-15] Subjective measures of the MBS of vaginal dryness and the MBS of dyspareunia were also shown here to significantly improve in the ITT and/or PP populations consistent with the previous studies.[13-15] A previous study of the MBS of vaginal dryness did not demonstrate significant improvement when ospemifene use was analyzed in women with an MBS of dryness in the ITT population.[15] This may be due to differences in power to detect improvements in vaginal dryness with ospemifene versus placebo between that previous study, which enrolled women with an MBS of vaginal dryness or dyspareunia, and our study, in which all enrolled women had an MBS of vaginal dryness. Different statistical analyses (last observation carried forward) compared with the MMRM approach and GEE modeling of this study may also have contributed to the different ITT results between studies. In addition, a large placebo effect observed by Portman et al[15] with a similar magnitude of ospemifene effect as the significant improvements reported by Bachmann and Komi,[13] may have also been confounding. Here we report significant improvements in vaginal dryness in women with a vaginal dryness MBS, even with allowing lubricant use, which was similar between the ospemifene and placebo groups.

The significantly greater proportion of clinical responders with ospemifene compared with placebo found here is similar to the proportion of responders previously reported.[15] While the response rate with ospemifene was only 32% at week 12, many fewer women responded to placebo (6%). This 32% response rate can be considered high given the very strict criteria for women to be responders in this study; those who had significant improvements in all three criteria: MV ($\geq$10 points), vaginal pH ($\geq$0.5 points), and vaginal dryness ($\geq$1 point). Because the definition of responders includes both objective and subjective parameters, the vaginal dryness improvements with ospemifene are likely clinically relevant. Satisfaction results further supported clinical relevance with 70% being very/moderately satisfied with ospemifene (vs 54% with placebo), and twice as many participants moderately/very dissatisfied in the placebo group (22%) compared with the ospemifene group (11%; Fig. 6). The response to

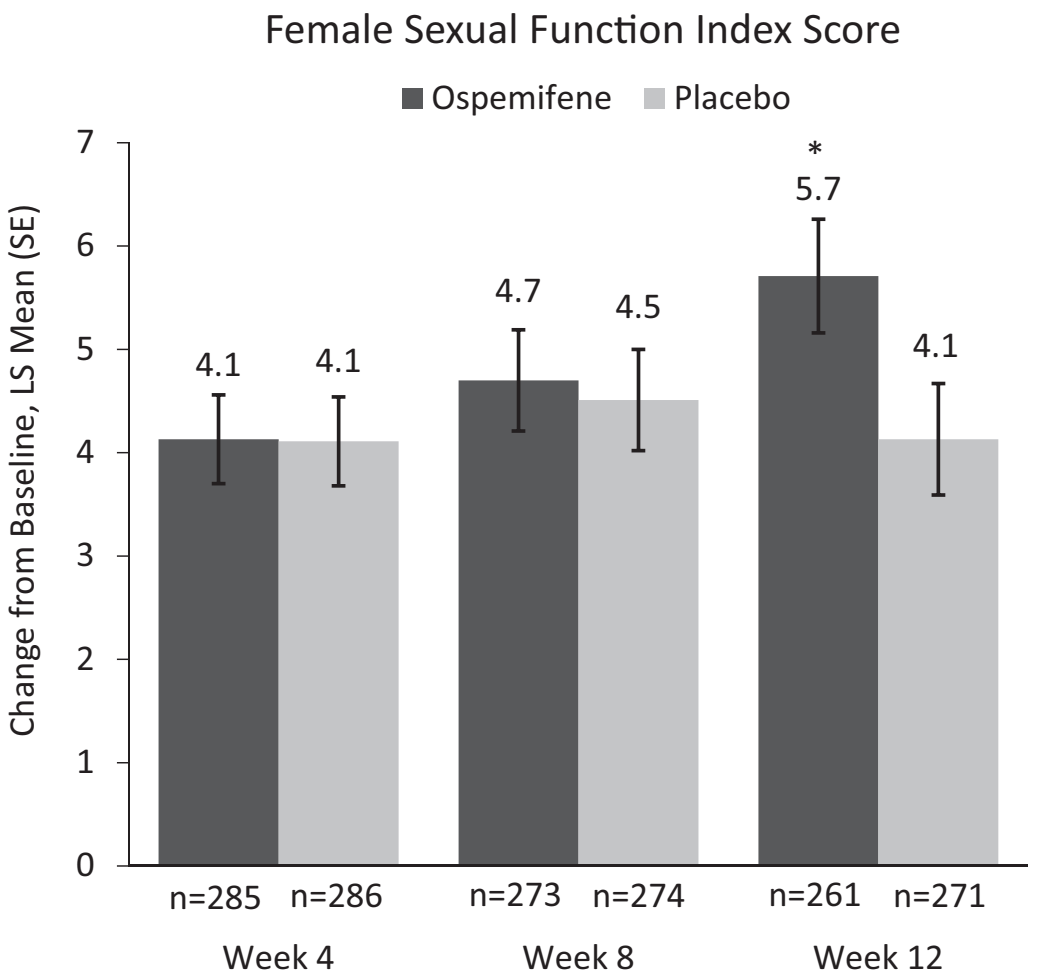

FIG. 5. Change from baseline in Female Sexual Function Index total score with ospemifene and placebo at weeks 4, 8, and 12. $^{*}P = 0.0392$ versus placebo.

ospemifene is not unexpected because there will always be some women who do not respond to any particular therapy.

Ospemifene was safe, well tolerated, and associated with rates of TEAEs similar to those observed with placebo in the present study, confirming the findings of previous phase 3 studies.[13-15] In addition, no new clinically important or unexpected treatment-related AEs were reported over 12 weeks. As in previous studies of ospemifene, hot flush was the most commonly reported TEAE. However, considering the age and proximity to menopause of many women in the study, hot flush rates were low. Moreover, very few women (n = 4 total) discontinued treatment due to this TEAE. None of the serious TEAEs were considered related to treatment, including the 1 acute myocardial infarction reported in the ospemifene group, which occurred in a woman with risk factors for cardiovascular disease, and no thromboembolic events were reported.

Endometrial safety is an important consideration for products that have estrogenic effects. Endometrial thickness and histology found in this study is consistent with that noted in other studies in which ospemifene was not associated with clinically significant changes in endometrial tissue or other estrogenic effects after 12 or 52 weeks of therapy.[13,15,18,20] No endometrial hyperplasia or cancer was observed in this study. Two 52-week endometrial safety studies[18,20] confirmed that ospemifene was associated with minimal endometrial stimulation, with only one case of simple hyperplasia observed, representing a rate (0.3%) substantially lower than the FDA requirement of less than 1%.[18]

This current study has several limitations. First, the duration of the trial was relatively short, but was as per regulatory guidance for efficacy and safety studies for moderate to severe vaginal symptoms. In addition, although all endometrial changes occurred in the active group mostly at 12 weeks, two 52-week endometrial safety studies confirmed that ospemifene was associated with minimal endometrial stimulation.[18,20] Another limitation is that the study's inclusion criteria were narrowly defined, suggesting that the population in this study may not be entirely representative of the general population of postmenopausal women. Most of the women in the study were white, in good health, and had a mean body

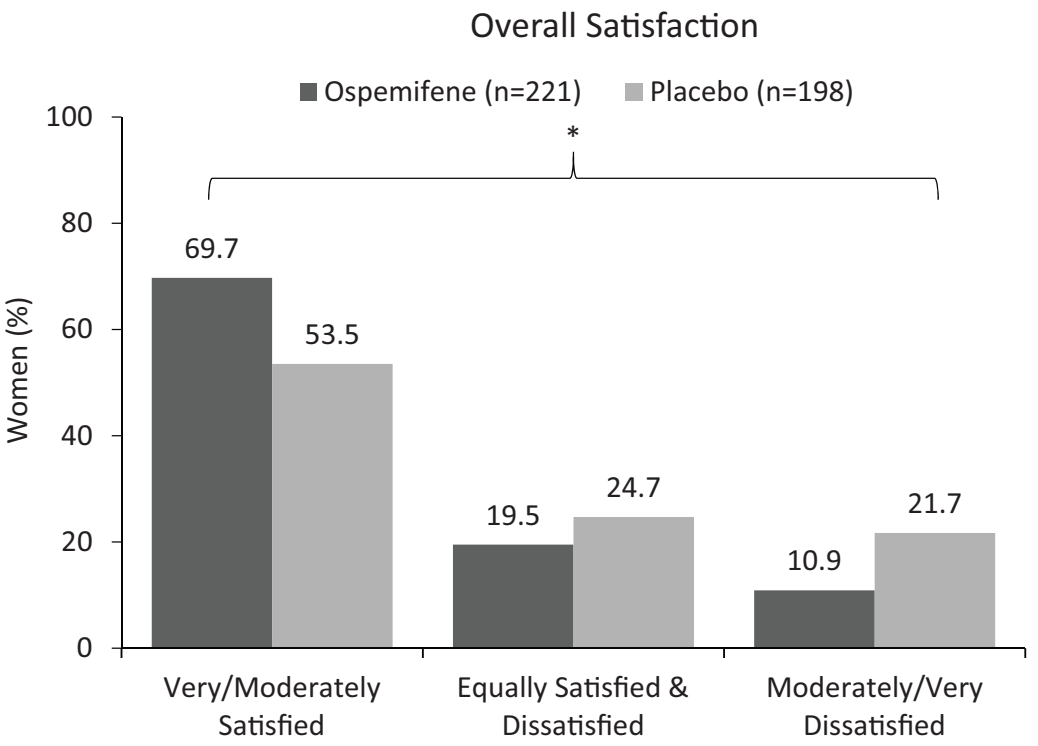

FIG. 6. Overall satisfaction with ospemifene and placebo at week 12 (ITT population). $^{*}P = 0.0007$ versus placebo for overall distribution using Wilcoxon rank-sum test. ITT, intent-to-treat.

mass index of 27 kg/m^2. Moreover, many women who have vaginal dryness may have other vaginal symptoms that could potentially worsen over the course of the study. Thus, studies that use MBS—an FDA recommended endpoint for clinical trials—may not adequately evaluate or address the multiple symptoms associated with VVA in postmenopausal women.[15,23] In addition, MBS is a subjective, patient-reported endpoint that may be influenced by a greater placebo effect than more objective endpoints.[23] Women were also given a nonhormone lubricant to be used as needed throughout the current study and in the previous phase 3 trials of ospemifene.[13-15] Such as-needed use of lubricant in these studies may confound the assessment of the subjective symptom of vaginal dryness with treatment.[15] Furthermore, the placebo-treated group (essentially an as-needed, lubricant-treated group) may make it more difficult to observe a statistically significant difference when assessing vaginal

TABLE 3. *Incidence of treatment-emergent adverse events in the safety population*

	Ospemifene (n = 317)	Placebo (n = 310)
Any TEAE, n (%)	112 (35.3)	103 (33.2)
Most common AEs[a], n (%)		
Hot flushes	20 (6.3)	8 (2.6)
Upper respiratory tract infection	7 (2.2)	11 (3.5)
Urinary tract infection	7 (2.2)	10 (3.2)
Bronchitis	7 (2.2)	4 (1.3)
Nasopharyngitis	4 (1.3)	8 (2.6)
Headache	5 (1.6)	7 (2.3)
Treatment-related AEs	28 (8.8)	20 (6.5)
Discontinuations due to AEs	5 (1.6)	3 (1.0)
Serious TEAEs	5 (1.6)	3 (1.0)
Treatment-related serious AEs	0 (0)	0 (0)

AE, adverse events; TEAE, treatment-emergent adverse events.
[a]In >2.0% of participants in either group.

TABLE 4. *Endometrial thickness and endometrial histology classifications at baseline and after 12 weeks of ospemifene or placebo in women with a uterus (safety population)*

	Ospemifene	Placebo
Endometrial thickness, mean (mm) ± SD		
Baseline	2.22 ± 0.80 (n = 130)	2.09 ± 0.82 (n = 129)
Week 12	2.81 ± 1.60 (n = 94)	1.91 ± 0.83 (n = 93)
Change	0.63 ± 1.59 (n = 94)	−0.23 ± 0.85 (n = 93)
Endometrial histology classification, n (%)		
Baseline	(n = 128)	(n = 128)
Active proliferation	1 (0.8)	0 (0)
Atrophy	89 (69.5)	80 (62.5)
Inactive	4 (3.1)	6 (4.7)
Weakly proliferative	2 (1.6)	1 (0.8)
Unsatisfactory biopsy[a]	32 (25.0)	41 (32.0)
Week 12	(n = 90)	(n = 89)
Active proliferation	5 (5.6)	0 (0)
Atrophy	24 (26.7)	59 (66.3)
Inactive	24 (26.7)	5 (5.6)
Weakly proliferative	11 (12.2)	1 (1.1)
Polyp	1 (1.1)	0 (0)
Unsatisfactory biopsy[a]	25 (27.8)	24 (27.0)

SD, standard deviation.
[a]Unsatisfactory biopsy because limited endometrial surface obtained, no endometrium present, or too scant for reliable diagnosis.

dryness versus ospemifene, as demonstrated by a previously reported higher placebo effect with this endpoint (-1.1 ± 1.02).[15] Nonetheless, statistically and clinically significant beneficial effects on the signs and symptoms of VVA were observed with ospemifene in this study.

CONCLUSIONS

Vaginal dryness, the most commonly reported symptom of postmenopausal VVA,[5-8,10] is often overlooked and undertreated, possibly due to a lack of information about available therapies, the avoidance of women and healthcare practitioners of discussing VVA, and/or dissatisfaction with currently available products. Here we confirm the positive physiologic effects of ospemifene on VVA and demonstrate its significant improvements on the MBS of vaginal dryness without any new or unexpected safety signals. Such efficacy data are exemplified by significant improvements with ospemifene relative to placebo in the percentages of vaginal superficial and parabasal cells, vaginal pH, and vaginal dryness severity first seen at 4 weeks and maintained up to 12 weeks, as well as significantly improved dyspareunia, MV, and FSFI total score and higher response and satisfaction rates with ospemifene versus placebo. With the negative impact of VVA and its related symptoms of vaginal dryness and dyspareunia on quality of life, and the preference of many women for oral therapies, ospemifene may be a useful treatment option for postmenopausal women with these VVA symptoms.

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