

Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial

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ABSTRACT

Background Ospemifene is a non-estrogen, tissue selective estrogen receptor agonist/antagonist, or selective estrogen receptor modulator, recently approved for the treatment of dyspareunia, a symptom of vulvar and vaginal atrophy (VVA), due to menopause. Postmenopausal dyspareunia is often associated with female sexual dysfunction (FSD). In this report, we present data that demonstrate the effect of ospemifene 60 mg/day on FSD assessed by the Female Sexual Function Index (FSFI), a widely used tool with six domains (Arousal, Desire, Orgasm, Lubrication, Satisfaction, and Pain).

Methods A phase-3, randomized, double-blind, 12-week trial ($n = 919$) compared the efficacy and safety of oral ospemifene 60 mg/day vs. placebo in postmenopausal women with VVA in two strata based on self-reported, most bothersome symptom of either dyspareunia or dryness. Primary data were published previously. We report herein pre-specified secondary efficacy endpoints analyses, including changes from baseline to Weeks 4 and 12 for FSFI total and domain scores as well as serum hormone levels.

Results Ospemifene 60 mg/day demonstrated a significantly greater FSFI total score improvement vs. placebo at Week 4 ($p < 0.001$). Improvement in FSFI scores continued to Week 12 ($p < 0.001$). At Week 4, the FSFI domains of Sexual Pain, Arousal, and Desire were significantly improved with ospemifene vs. placebo; at Week 12, improvements in all domains were significant ($p < 0.05$). Changes in serum hormones were minor and uncorrelated with changes in sexual functioning.

Conclusion In a large, randomized, double-blind, placebo-controlled trial, ospemifene 60 mg/day significantly improved FSD in women with VVA. Consistent effects across FSFI domains were observed.

INTRODUCTION

Vulvar and vaginal atrophy (VVA) is a chronic, progressive medical condition that is associated with physiological changes of the vagina and symptoms such as dyspareunia and vaginal dryness. It is estimated that VVA affects up to approximately 40–50% of postmenopausal women^{1,2}. Women can now expect to spend more than one-third of their lives in a

postmenopausal state due to an increased life expectancy^{3,4}. Therefore, the proper diagnosis and treatment of VVA have become increasingly important in the care of postmenopausal women⁵.

Multiple studies have demonstrated the negative impact of VVA on quality of life and sexual function in postmenopausal women^{1,2}. REVIVE, a survey of 3046 menopausal women, found that VVA significantly interferes with overall

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healthy sexual functioning⁶. A separate study, the Menopause Epidemiology study, evaluated 1480 postmenopausal women; respondents reporting sexual dysfunction were 3.84 times more likely to have VVA⁷. The CLOSER survey found that VVA-related painful sex negatively affected relationships for both male and female partners⁸, and a survey of 363 sexually active women found that more frequent dyspareunia was associated with less frequent sexual intercourse⁹.

Currently available treatment options for postmenopausal VVA include over-the-counter products (e.g. vaginal lubricants and moisturizers), systemic hormonal therapies (when treatment of other menopausal symptoms is needed), vaginal estrogen therapies (intravaginal tablets, rings, and creams), and ospemifene (for dyspareunia)¹⁰. Oral and local estrogen therapies have been reported to improve sexual functioning in some studies but not in others. The reasons for the inconsistent findings are not clear. One hypothesis is that the increase in sex hormone binding globulin (SHBG) levels after oral estrogen therapies results in a decreased bioavailability of testosterone, which may impact the assessment of sexual function^{11–13}.

Various assessment tools have been used to measure factors associated with female sexual dysfunction (FSD). The Female Sexual Function Index (FSFI) was developed as a brief, easy-to-administer, self-report tool for assessing key dimensions or domains of sexual function and quality of life (Arousal, Desire, Orgasm, Lubrication, Satisfaction, and Pain) in various populations of women¹⁴. The FSFI questionnaire has been used in postmenopausal women, although it has not been specifically validated in a VVA population. Other assessment tools were developed prior to the revision of sexual disorder classifications but do not address some aspects of the current definitions. For example, to increase clinical relevance, the FSFI domains of Desire and Arousal were separated to allow factors such as lubrication or subjective arousal/desire to be measured as separate, nuanced responses to sexual stimulation.

Ospemifene is an oral, non-estrogen, tissue selective estrogen agonist/antagonist approved in the United States for the treatment of moderate to severe dyspareunia associated with VVA due to menopause¹⁵. A phase-3, randomized, double-blind clinical trial assessed the efficacy, safety, and tolerability of ospemifene in the treatment of postmenopausal VVA^{16,17}. Here, we report data on the effect of ospemifene on sexual function as evaluated by the FSFI and data on changes in

serum hormones, which were pre-specified, secondary efficacy endpoints of this study.

METHODS

Study design

This study was a phase-3, multicenter, randomized, double-blind, parallel-group trial comparing ospemifene 60 mg/day administered for 12 weeks with placebo in postmenopausal women with VVA who were stratified by a self-reported most bothersome symptom (MBS) of either dyspareunia or vaginal dryness. The co-primary endpoints of the trial have been previously reported^{16,17}. Among the secondary efficacy endpoints were change from baseline in total score (at Weeks 4 and 12), change from baseline in the domains of the FSFI (at Weeks 4 and 12), and change from baseline in serum sex hormones (at Week 12).

FSFI assessments

Study participants completed the FSFI questionnaire at baseline, Week 4, and Week 12 (or last observation carried forward, LOCF). The questionnaire consisted of 19 questions, each rated on a scale ranging from 0 to 5 or 1 to 5, with 0 indicating no sexual activity in the past month (Table 1)¹⁴. Scores for each of the six domains were calculated in the standard fashion by adding individual domain question scores and multiplying by the domain factor (i.e. 0.6 for Desire, 0.3 for Arousal and Lubrication, and 0.4 for Orgasm, Satisfaction, and Pain). The total FSFI score is the sum of the scores for the six individual domains. Of a total possible score of 36, 26.55 or less is considered to constitute sexual dysfunction in a population of premenopausal and postmenopausal women¹⁸. No cut-off score for FSD has been described specifically in a VVA population with dyspareunia or dryness.

Assessment of serum hormones

Fasting serum samples were collected at screening and Week 12 or final visit. Specimens were prepared at the sites (clot

Table 1 Female Sexual Function Index scoring system. A domain score of zero indicates that no sexual activity was reported during the past month. From: Rosen R, et al. *J Sex Marital Ther* 2001;26:191–208. Available at <http://www.fsfi-questionnaire.com/>

Domain	Questions	Score range	Factor	Minimum score	Maximum score
Desire	1, 2	1–5	0.6	1.2	6
Arousal	3, 4, 5, 6	0–5	0.3	0	6
Lubrication	7, 8, 9, 10	0–5	0.3	0	6
Orgasm	11, 12, 13	0–5	0.4	0	6
Satisfaction	14, 15, 16	0 (or 1)–5	0.4	0	6
Pain	17, 18, 19	0–5	0.4	0	6
Full scale score range				2	36

time of 15–30 min and centrifugation at 3000 rpm to separate serum) and were shipped on dry ice on the day of collection to a central laboratory (Mayo Clinic, Rochester, MN, USA). Serum levels of the following analytes were measured: estradiol, follicle stimulating hormone (FSH), luteinizing hormone (LH), SHBG, and total and free testosterone. Analysis of FSH, LH, and SHBG was conducted using chemiluminescent immunoassays; analysis of estradiol and testosterone was conducted using liquid chromatography–mass spectrometry.

Statistical analyses

Analyses of FSFI data were conducted for the intent-to-treat (ITT) population (all randomized subjects who had received \geq one dose of the study medication) and for the dyspareunia and dryness strata. A *post hoc* analysis also evaluated the change from baseline to Weeks 4 and 12 in FSFI total and domain scores for the subgroups of hysterectomized and non-hysterectomized women for the combined strata among the ITT population.

Separate analysis of covariance (ANCOVA) models were used for the by-stratum and combined strata analyses for change in FSFI total score and domain scores to Weeks 4 and 12. For analysis of each separate stratum, an ANCOVA model was used (i.e. with treatment and center as fixed effects in the model and the baseline value used as the covariate). For combined data, the ANCOVA included stratum, rather than center, as a fixed effect in the model. An additional analysis, including treatment by stratum interaction, was also performed to test for the generalizability of results across the strata.

RESULTS

Participant disposition

A total of 919 women were randomized; 463 participants received ospemifene 60 mg/day and 456 received placebo. Approximately two-thirds of participants ($n = 605$) reported dyspareunia as the MBS; 303 of these women were treated with ospemifene and 302 received placebo. Approximately one-third of participants ($n = 314$) reported dryness as the MBS; 160 of these women were treated with ospemifene and 154 received placebo. Overall, the mean (standard deviation) age of participants was 58.6 (6.47) years, the majority of participants were white, and approximately half of the participants (53.1%) had an intact uterus. Demographic and baseline characteristics were balanced between treatment groups, both in the ITT population (Table 2) and in each of the two strata.

Of the 919 randomized participants, 819 women (89.1%) completed the study. The percentage of women who discontinued from the study was 10.2% for the ospemifene group and 11.6% for the placebo group; adverse events were the most common reason for discontinuation (5.4% vs. 3.1%, respectively). The dispositions of participants were similar in

Table 2 Demographic and baseline characteristics of the intent-to-treat (ITT) population. The ITT population included all randomized participants who received \geq one dose of study medication. Data are given as mean \pm standard deviation or n (%)

Parameter	Ospemifene 60 mg/day ($n = 463$)	Placebo ($n = 456$)
Age (years)	58.7 \pm 6.56	58.5 \pm 6.39
Race		
White	409 (88.3)	396 (86.8)
Black or African American	28 (6.0)	35 (7.7)
other	26 (5.6)	25 (5.5)
Body mass index (kg/m ²)	26.16 \pm 4.31	26.21 \pm 4.32
Intact uterus	$n = 463$	$n = 455$
yes	242 (52.3)	245 (53.8)
no	221 (47.7)	210 (46.2)
FSFI total score at baseline	19.84 \pm 5.97	19.55 \pm 6.07

FSFI, Female Sexual Function Index

both strata compared with the overall population. As reported previously, this study met the co-primary efficacy endpoints of changes from baseline to Week 12 in the percentage of superficial cells and parabasal cells, vaginal pH, and the severity of dyspareunia as the MBS¹⁶.

Sexual function: FSFI total score

In the ITT population, women who received oral ospemifene 60 mg/day had a significantly greater improvement in the FSFI total score compared with women who received placebo (Figure 1). This improvement was evident at Week 4 ($p < 0.001$) and continued to increase in magnitude up to Week 12 (LOCF; $p < 0.001$).

In the dyspareunia stratum, significant improvements in FSFI total score were observed in women treated with ospemifene compared with placebo at Weeks 4 ($p < 0.001$) and 12 (LOCF; $p < 0.0001$; Figure 2). In the vaginal dryness

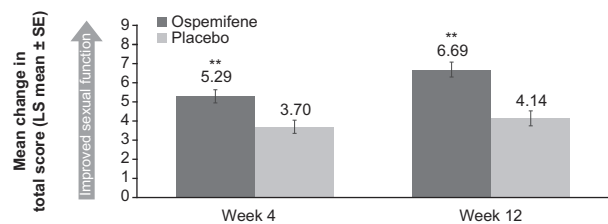


Figure 1 Change from baseline to Weeks 4 and 12 (last observation carried forward) in the Female Sexual Function Index (FSFI) total score in the intent-to-treat (ITT) population. **, $p < 0.001$ compared with placebo. p Values were computed using ANCOVA where change from baseline was the response variable, baseline assessment was the covariate, and treatment and stratum were fixed effects. The ITT population included all randomized participants who received \geq one dose of study medication. ANCOVA, analysis of covariance; LS, least squares

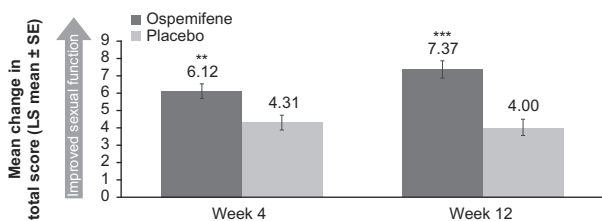


Figure 2 Change from baseline to Weeks 4 and 12 (last observation carried forward) in the Female Sexual Function Index (FSFI) total score in the dyspareunia stratum. **, $p < 0.001$ compared with placebo; ***, $p < 0.0001$ compared with placebo. p Values were computed using ANCOVA where change from baseline was the response variable, baseline assessment was the covariate, and treatment and center were fixed effects. ANCOVA, analysis of covariance; LS, least squares

stratum, improvements in FSFI total score were numerically greater in women treated with ospemifene compared with placebo at Weeks 4 and 12 (LOCF); however, the difference did not reach statistical significance (data not shown).

Total scores for the FSFI were also evaluated in a subgroup analysis of women with or without an intact uterus. In the subgroup with an intact uterus, those treated with ospemifene 60 mg/day showed significantly greater improvements than those randomized to placebo at both Weeks 4 ($p = 0.0022$) and 12 (LOCF; $p < 0.0001$). In the subgroup without an intact uterus, the difference between ospemifene and placebo was significant at Week 12 (LOCF; $p = 0.0133$; data not shown).

Sexual function: FSFI domain scores

In the ITT population, greater improvements were observed in all six FSFI domains in women treated with ospemifene 60 mg/day compared with placebo (Figure 3). At Week 4, statisti-

cally significant improvements were noted for the FSFI domains of Desire, Arousal, and Pain (all $p < 0.05$) and Lubrication ($p < 0.001$). The domain improvements noted in women treated with ospemifene continued to increase in magnitude and reached statistical significance in all domains compared with placebo by Week 12 (LOCF).

In the dyspareunia stratum, the same pattern of treatment effect was observed, with statistically significant improvements in all domains at Week 12 (Figure 4; $p < 0.05$, $p < 0.001$, or $p < 0.0001$). In the dryness stratum, improvements in FSFI domain scores at Weeks 4 and 12 were numerically greater in women in the ospemifene group than in the placebo group; however, statistical significance was not achieved (data not shown).

In participants with a history of hysterectomy, improvements at Week 4 were significant in the domains of Lubrication ($p = 0.0148$) and Pain ($p = 0.0151$); for women with an intact uterus, improvements were significant in four domains (Desire ($p = 0.0174$), Lubrication ($p = 0.0002$), Orgasm ($p = 0.0118$), and Pain ($p = 0.020$)). Improvements were sustained from Week 4 to Week 12 (LOCF) for both women with an intact uterus and those without. These improvements were significant at Week 12 (LOCF) in the subpopulation of hysterectomized women for the three domains of Desire ($p = 0.0188$), Lubrication ($p = 0.0023$), and Pain ($p = 0.0413$), and significant for all domains at Week 12 (LOCF; $p < 0.05$) in the subpopulation of non-hysterectomized women.

Serum hormones

For the women in the ospemifene group, both mean FSH and LH levels decreased slightly from baseline to Week 12 while remaining well within the normal range for postmenopausal women. There were no clinically relevant changes in mean estradiol levels after treatment with ospemifene. The mean

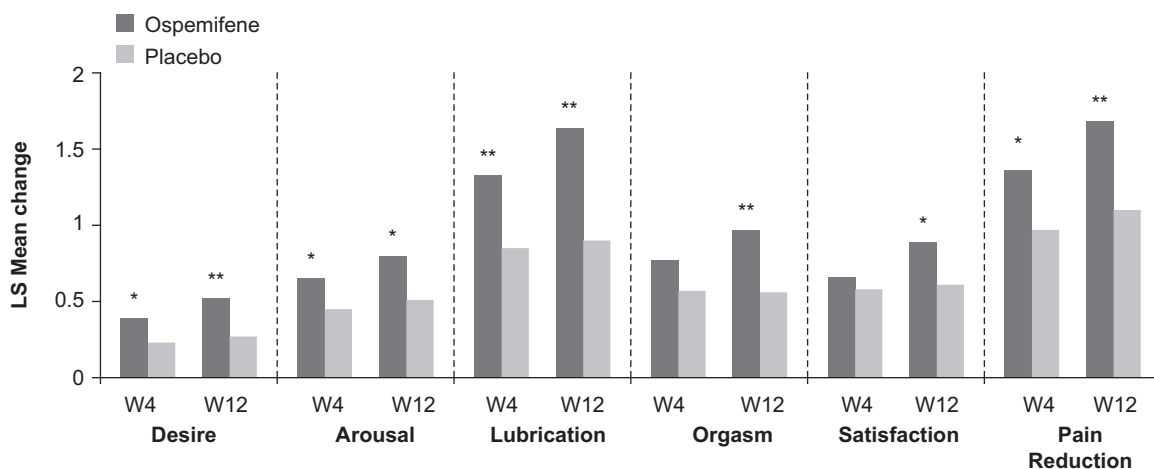


Figure 3 Change from baseline to Weeks 4 and 12 (last observation carried forward) in the Female Sexual Function Index (FSFI) domain scores in the intent-to-treat (ITT) population. *, $p < 0.05$ compared with placebo; **, $p < 0.001$ compared with placebo. p Values were computed using ANCOVA where change from baseline was the response variable, baseline assessment was the covariate, and treatment and stratum were fixed effects. ANCOVA, analysis of covariance; LS, least squares; W4, Week 4; W12, Week 12

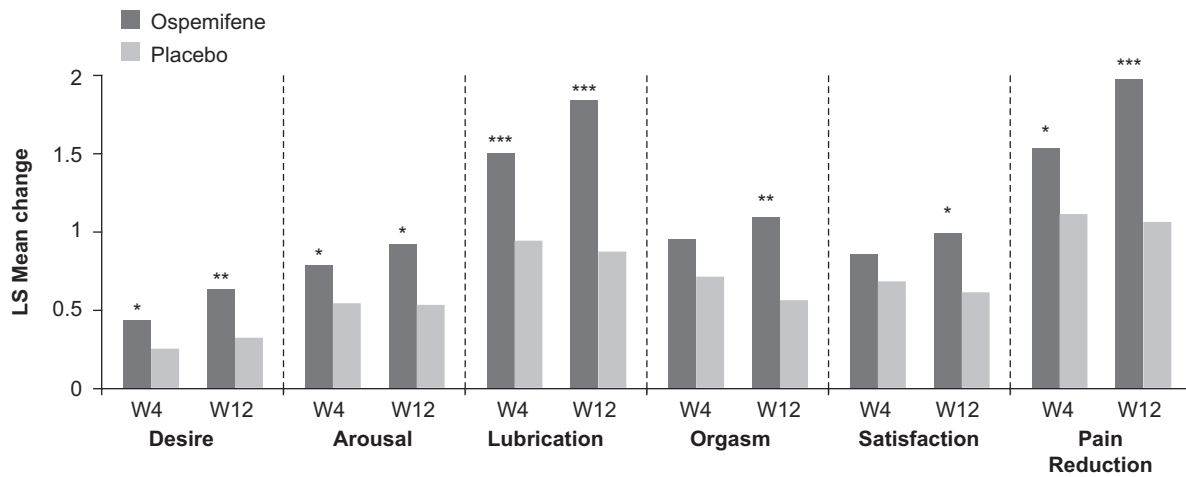


Figure 4 Change from baseline to Weeks 4 and 12 (last observation carried forward) in the Female Sexual Function Index (FSFI) domain scores in the dyspareunia stratum. *, $p < 0.05$ compared with placebo; **, $p < 0.001$ compared with placebo; ***, $p < 0.0001$ compared with placebo. p Values were computed using ANCOVA where change from baseline was the response variable, baseline assessment was the covariate, and treatment and center were fixed effects. ANCOVA, analysis of covariance; LS, least squares; W4, Week 4; W12, Week 12

SHBG level increased, but remained within the normal range at Week 12 (20–130 nmol/l). One ospemifene participant in the dryness stratum and 25 participants (24 ospemifene, one placebo) in the dyspareunia stratum shifted from normal SHBG levels at baseline to higher than normal levels at Week 12. Total testosterone levels increased slightly in women in the ospemifene group; however, mean free testosterone levels remained unchanged (Figure 5).

These symptoms are directly related to the physiological changes of the vaginal epithelium (e.g. thinning, narrowing, reduced elasticity, and increased vaginal pH) due to a decrease in circulating estrogen levels after menopause¹⁹. The link between postmenopausal VVA and FSD has been demonstrated^{7,8}. An epidemiologic study in sexually active postmenopausal women examined the relationship between VVA (defined as pain, itching, and dryness associated with sexual activity) and sexual dysfunction (desire, arousal, and orgasm) using the Arizona Sexual Experience questionnaire⁷. The prevalences of sexual dysfunction (55%) and VVA (57%) were similar and there was substantial overlap of the two conditions (40% of the study participants had both conditions). The authors of that study concluded that the pain

DISCUSSION

It is estimated that up to approximately 40–50% of postmenopausal women experience symptoms of VVA^{1,2,6}.

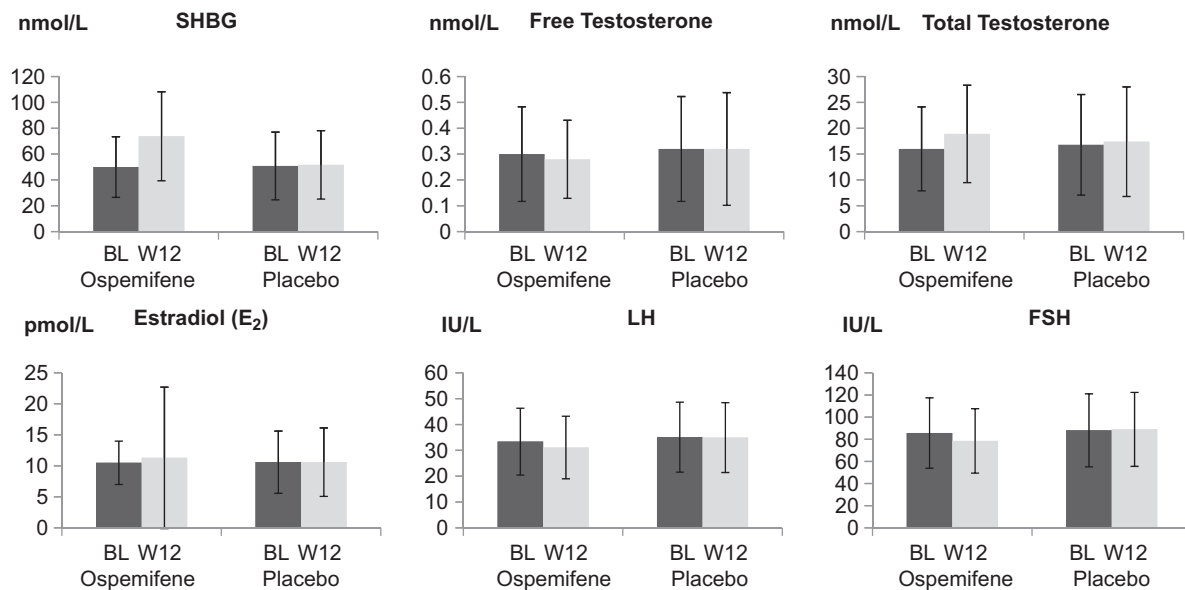


Figure 5 Mean \pm standard deviation serum hormone concentrations at baseline and Week 12 in the intent-to-treat population. BL, baseline; FSH, follicle stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin; W12, Week 12

associated with VVA may preclude women from desiring, initiating, or responding to sexual activity. Nonetheless, 52% of menopausal women aged 50–79 years in the Women's Health Initiative Observational study reported that they had been sexually active with a partner in the past year²⁰, and most published literature suggests that approximately 10–30% of women over 70 years of age still engage in sexual intercourse²¹.

Therefore, one may hypothesize that therapies aimed at improving VVA symptoms may help maintain life-long sexuality and potentially improve sexual function. A recent Cochrane review²² found that estrogen alone or in combination with progestogens (EPT) was associated with a small to moderate improvement in sexual function, and the review reported data on selective estrogen receptor modulators and sexual function to be limited and inconclusive. Some studies with EPT have also failed to detect corresponding improvements in sexual satisfaction, even when VVA was improved²³. Importantly, since the Women's Health Initiative, substantial numbers of women have declined to initiate or continue estrogen-based therapies and are seeking alternatives²⁴.

Ospemifene, an oral non-estrogen drug with tissue-selective estrogen agonist/antagonist effects, exerts an agonistic effect on vaginal epithelial tissue^{15,25}. Previously published results of this phase-3 trial demonstrated that ospemifene 60 mg/day was effective in improving physiological vaginal changes (maturation index and pH)^{16,17} and, for participants with an MBS of dyspareunia, significantly reduced the severity of dyspareunia¹⁶.

This trial also evaluated the effect of ospemifene on FSFI scores, a pre-specified secondary efficacy endpoint, as reported in the current article. Treatment with ospemifene led to significantly greater improvements, compared with placebo, in total FSFI composite score and individual FSFI domain scores for the ITT population. In general, improvements were observed as early as Week 4 and continued to increase in magnitude up to Week 12. Although underpowered, exploratory subgroup analyses were carried out to evaluate dyspareunia and dryness strata, in hysterectomized as well as non-hysterectomized participants. Statistically significant improvements in FSFI scores were observed in the dyspareunia stratum. However, women in the vaginal dryness stratum had numerical improvements in FSFI scores that did not reach statistical significance. Both subgroups of women, with or without an intact uterus, had significant improvements in FSFI scores with ospemifene treatment. Overall, results were highly consistent across FSFI domains and patient subgroups.

Serum levels of some hormones (e.g. testosterone and dehydroepiandrosterone) are known to affect FSFI scores^{16,26,27}. In the current study, clinically non-relevant increases in mean total testosterone and moderate increases in mean SHBG were observed in women receiving ospemifene; mean estradiol and free testosterone levels were unchanged, whereas mean FSH and LH levels had a clinically non-relevant decrease with ospemifene treatment. These data suggest that the significant improvements in FSFI scores noted in women treated with ospemifene were unlikely to be attributed to changes in

serum sex hormone levels, but rather appear to be due to the positive effects of ospemifene on the physiology of the vaginal epithelium (maturation index and vaginal pH) and the VVA symptom of dyspareunia. It is important to note that treatment with ospemifene resulted in improvement not only in pain and lubrication, but also in the scores in all six FSFI domains. Since a systemic non-steroidal ligand such as ospemifene might have selective genomic or non-genomic effects on genital, extragenital, and central nervous system tissues, other potential central and peripheral mechanisms for the improved sexual response and function demonstrated here deserve further study²⁸.

The data reported here have several limitations. First, although the FSFI is a widely used tool that has been documented in more than 700 publications and validated in the postmenopausal population, it has not been validated specifically in a VVA population such as the one analyzed here. Second, the change in FSFI score was pre-specified as a secondary efficacy endpoint for this phase-3 trial but was not a primary outcome. Third, the subgroup analyses presented here were underpowered and were performed solely for hypothesis generation. Fourth, the FSFI data are based on patient self-reported diaries with the known potential inconsistencies of diary data. Additionally, the evaluation of serum hormones could have potentially been imprecise due to the inexact timing of sample collection.

CONCLUSIONS

In a phase-3 randomized, double-blind, placebo-controlled, 12-week clinical trial, oral ospemifene 60 mg/day demonstrated significant improvements in the co-primary endpoints of physiological vaginal changes in postmenopausal women with VVA due to menopause and reduced severity of dyspareunia. Treatment with ospemifene also significantly improved the total FSFI score and FSFI domain scores in the ITT population and in the dyspareunia stratum. There was no apparent relationship between serum hormone levels and changes in FSFI scores.

Conflict of interest GDC: Consultant for: Shionogi Inc.; SAK: Consultant for: Apricus, Emotional Brain, Palatin, Novo Nordisk, Shionogi Inc., Sprout, Pfizer, SST, and Teva; DJP: Consultant for: Shionogi Inc., Sprout, Palatin, Noven, Pfizer, Novo Nordisk, Actavis, Exploramed. Research Grants: QuatRx, Endoceutics, Trimel, Amneal, Sun, Pfizer, Bayer, Palatin, Actavis. Speaker's Bureau: Shionogi Inc., Noven, Pfizer, Teva, TherapeuticsMD; RCR: Research Support: Shionogi Inc., Pfizer Inc, Actavis. Consultant for: Palatin, Apricus, Sprout; SG: Former Employee of: Shionogi Inc.

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