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Long-term safety of ospemifene (52-week extension) in the treatment of vulvar and vaginal atrophy in hysterectomized postmenopausal women☆

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ABSTRACT

Objective: To examine the long-term safety of oral ospemifene, a non-estrogen tissue-selective estrogen agonist/antagonist, for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy (VVA) due to menopause.
Study design: This multicenter, long-term, open-label, safety extension study was conducted in women without a uterus aged 40–80 years ($N = 301$) who received oral ospemifene 60 mg/day for 52 weeks. Participants either continued their 60-mg/day ospemifene dose from the initial 12-week pivotal efficacy study or switched from blinded placebo or ospemifene 30 mg/day to open-label ospemifene 60 mg/day. The 52-week open-label extension period plus initial 12-week treatment period totaled up to 64 weeks of ospemifene exposure. A 4-week posttreatment follow-up ensued (68 weeks total).
Main outcome measures: Safety assessments included adverse events, laboratory studies, physical and gynecologic examination, vital signs, breast palpation, and mammography.
Results: Most treatment-emergent adverse events (TEAEs) during the extension study were mild or moderate in severity. The most common TEAE related to study drug was hot flushes (10%; leading to discontinuation for 2% of patients). One serious TEAE, a non-ST-elevation myocardial infarction in a patient with pre-existing cardiac disease, was considered possibly related to study medication. One mild breast-related TEAE, considered unrelated to study drug, was ongoing at study completion. There were no instances of pelvic organ prolapse, incontinence, venous thromboembolism, fractures, breast cancers or death. No clinically significant adverse changes were observed in other safety parameters.
Conclusions: Ospemifene is clinically safe and generally well tolerated in postmenopausal patients with dyspareunia, a symptom of VVA.

1. Introduction

Vulvar and vaginal atrophy (VVA) is a chronic and often progressive condition that affects approximately 50% of postmenopausal women [1–5]. Despite the high prevalence of VVA, this condition is often undiagnosed or inadequately treated [1–3]. Currently available treatment options include over-the-counter products (lubricants and moisturizers) that may provide some temporary symptom relief, but do not treat the physiological changes underlying VVA, which can lead to the development of symptoms such as dyspareunia [6–8]. Other treatment options include vaginal estrogen therapies, which are recommended to be used at the lowest effective dose for the shortest duration consistent with treatment goals and risks for the individual woman [4,9–12]. Given the limited number of options, additional treatment choices for physicians and patients are desirable [1,2].

Ospemifene, a tissue-selective estrogen agonist/antagonist (also known as a selective estrogen receptor modulator, SERM), is the first non-estrogen oral prescription alternative to estrogen therapies for the treatment of moderate to severe dyspareunia, a symptom of VVA due to menopause [13,14]. Ospemifene has multiple tissue-specific effects. Initial preclinical studies of ospemifene on bone structure and strength demonstrated that ospemifene has stimulatory effects on bone [15]. Additional preclinical studies showed that ospemifene treatment has anti-estrogenic effects

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in vitro and in vivo in human MCF-7 breast cancer cells [16,17]. To date, clinical trials on bone and breast endpoints have not been performed. Ospemifene has neutral to antagonistic activity on endometrial tissue [15]. The profile of ospemifene in clinical trials and in preclinical studies demonstrated beneficial effects on physiological changes in the vagina that are associated with VVA, while having selective agonist/antagonist effects in other tissues, and resulting in improvement of symptoms of dyspareunia in postmenopausal women [18,19].

In short- and long-term studies of postmenopausal women, ospemifene was shown to be effective for the treatment of moderate to severe symptoms associated with VVA [20–23]. In a 12-week, randomized, double-blind study in postmenopausal women ($N = 826$) comparing ospemifene 30 mg/day and 60 mg/day with placebo, ospemifene 60 mg/day demonstrated statistically significant improvement over placebo for all co-primary endpoints, including improvement from Baseline ("Baseline" refers to Day 1 of the initial 12-week study) in the percentages of superficial and parabasal cells ($p < .001$ for both), vaginal pH ($p < .001$), and severity of the most bothersome symptoms of VVA, including dyspareunia ($p = .023$) or dryness ($p = .021$) [20]. Ospemifene was generally well tolerated. The most frequently reported adverse events (AEs) were hot flushes, which were generally mild or moderate in severity and resulted in a low rate of discontinuation. Other commonly reported AEs included urinary tract infections and headaches. In addition to the 1-year safety extension study of ospemifene 60 mg reported herein, a separate 40-week safety extension was conducted in a cohort of women with an intact uterus ($n = 180$) who continued the randomized double-blind treatment that they had been assigned in the initial 12-week study (ospemifene 30 mg/day, ospemifene 60 mg/day, or placebo) [21].

During the extension period in the study of women with an intact uterus, no clinically significant adverse changes were observed from safety assessments, which included endometrial ultrasound and biopsy assessments; gynecologic examinations, mammograms, and Papanicolaou tests; physical examinations; vital signs; and safety laboratory values. Similar to the initial 12-week study, the most frequently reported treatment-related AE was hot flushes, which resulted in few discontinuations. Since several SERMs in development were associated with a significant 4-fold or greater increased incidence of pelvic organ prolapse and incontinence, treatment-emergent AEs (TEAEs) of this type are of particular interest, especially in a hysterectomized cohort [24,25]. No increased incidences of prolapse or incontinence were observed in hysterectomized women while taking ospemifene during this extension study. This report presents findings from a 52-week, open-label extension assessing the long-term safety of ospemifene 60 mg/day for the treatment of VVA in women without a uterus.

2. Methods

2.1. Study design

This multicenter, open-label, long-term safety extension study enrolled women without a uterus (ClinicalTrials.gov identifier: NCT01586364) who had participated in the initial 12-week, Phase 3, efficacy and safety study of ospemifene for the treatment of VVA in postmenopausal women (NCT00276094) [20] (Fig. 1A). The details of this initial study have been described elsewhere; however, a general summary is provided here. A randomized, double-blind study of 826 postmenopausal women with and without a uterus were randomized to receive ospemifene 30 or 60 mg/day or placebo (1:1:1) for 12 weeks. An additional, separate, long-term (52-week) extension study of women with a uterus has been completed and is described elsewhere [21]. This extension study included 301 women without a uterus. The duration of the open-label treatment extension was 52 weeks. During this extension, all patients were treated with ospemifene 60 mg/day regardless of treatment assignment in the initial 12-week study. The safety extension study concluded with a 4-week follow-up period. Thus, the duration of treatment plus the posttreatment follow-up period totaled 68 weeks (Fig. 1B).

The results of a separate long-term safety extension study (NCT01585558) of 180 postmenopausal women with an intact uterus, who completed the initial 12-week study and remained on double-blind treatment with ospemifene or on placebo, have been reported previously [21].

2.2. Patient population

All participants who entered the present open-label safety extension study were required to have completed the initial 12-week study. A detailed account of inclusion and exclusion criteria for the initial study has been reported previously [20]. Briefly, the women were required to be 40–80 years of age and postmenopausal (defined as at least 6 weeks elapsed since a bilateral oophorectomy, or, in the case of hysterectomized women with intact ovaries, follicle-stimulating hormone [FSH] levels ≥40 IU/L). Participants were also required to have the following signs and symptoms of VVA: ≤5% superficial cells on a vaginal smear (Maturation Index); vaginal pH >5.0; and at least 1 moderate or severe symptom of VVA (such as dyspareunia or vaginal dryness).

Exclusion criteria were as follows: body mass index (BMI) ≥37 kg/m^2; systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥100 mm Hg; clinically relevant abnormalities in safety laboratory tests (hematology, chemistry, urinalysis, coagulation parameters, serum lipid levels, and hormone levels) or electrocardiogram; clinically significant abnormal findings on complete pelvic examination, breast examination, or mammogram; suspicion or history of any malignancy within 10 years; or use of any hormone therapy (unless a sufficient washout period preceded any procedure).

Women who met the study criteria and had completed the initial 12-week study were eligible for the present 52-week extension study. Participants were excluded from the extension study if there were clinically significant abnormal findings at the Week 12 visit for the initial study or if they had any physical or psychiatric condition that could have interfered with their ability to adhere to the study procedures.

Written informed consent, including agreement to follow dosing regimens and attend all study visits, was obtained prior to enrollment. All participants received treatment with open-label, oral ospemifene 60-mg tablets, which were taken once daily in the morning with food. Institutional Review Board (IRB) approval was obtained for each study site, with a central IRB responsible for the initial and continuing review and approval of the clinical study and for complying with the requirements of section 21 of the Code of Federal Regulations (CFR), Part 56. The study was conducted in accordance with the guidelines of Good Clinical Practice, the Declaration of Helsinki, and all applicable local regulations. This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and current Good Clinical Practices and in compliance with local regulatory requirements and 21 CFR 312.

2.3. Safety assessments

A summary of safety assessments is provided in Fig. 2. AEs were documented at each study visit, and participants were instructed to spontaneously report any AEs occurring between

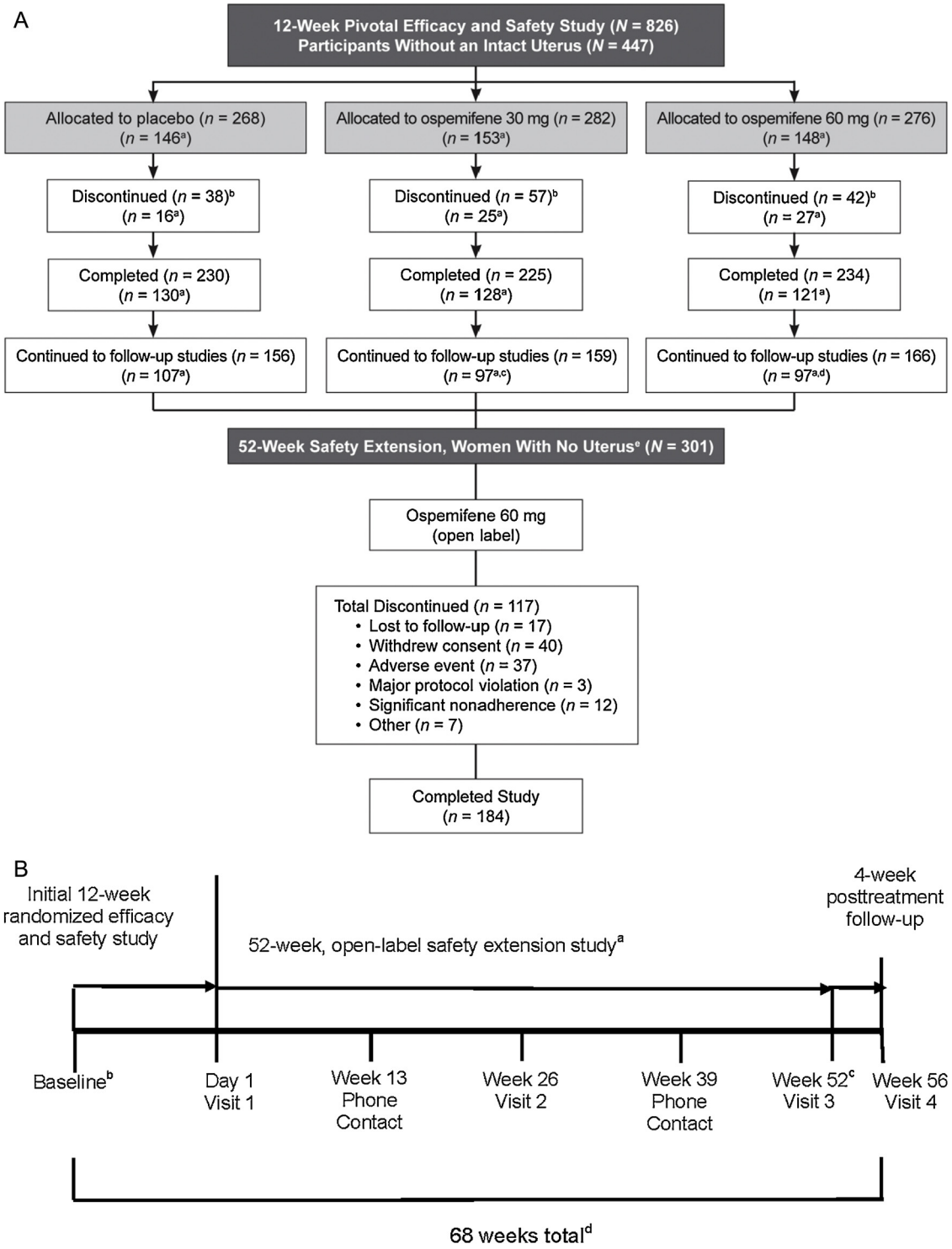

Fig. 1. (A) Study disposition (intent-to-treat population). [a]The number of participants without a uterus. [b]The number of participants with a uterus (reported separately) [21]. [c]Lost to follow-up; participant decision/consent withdrawal; adverse event; major protocol violation; participant used a concomitant medicinal product that may compromise safety or efficacy evaluations; significant noncompliance with treatment or study procedures; and any other reason as judged by the investigator. [d]One participant without a uterus on ospemifene 30 mg/day signed an informed consent form but did not enroll in the extension study. [e]One participant without a uterus on ospemifene 60 mg/day was moved to the extension study but did not sign an informed consent form and was not enrolled. [f]All participants without a uterus were treated with ospemifene 60 mg/day (patients who had been randomized to receive ospemifene 30 mg or placebo in the initial 12-week study were switched to ospemifene 60 mg). (B) Timeline of the 52-week safety extension of a 12-week efficacy and safety study in postmenopausal women. [a]Patients in the extension study included only those without an intact uterus. [b]"Baseline" in the 52-week extension study for safety and visual evaluation parameters refers to Baseline in the initial 12-week study. [c]Or discontinuation. [d]The total treatment period for the safety study was 52 weeks, followed by a 4-week posttreatment follow-up period (68 weeks total, including the initial study).

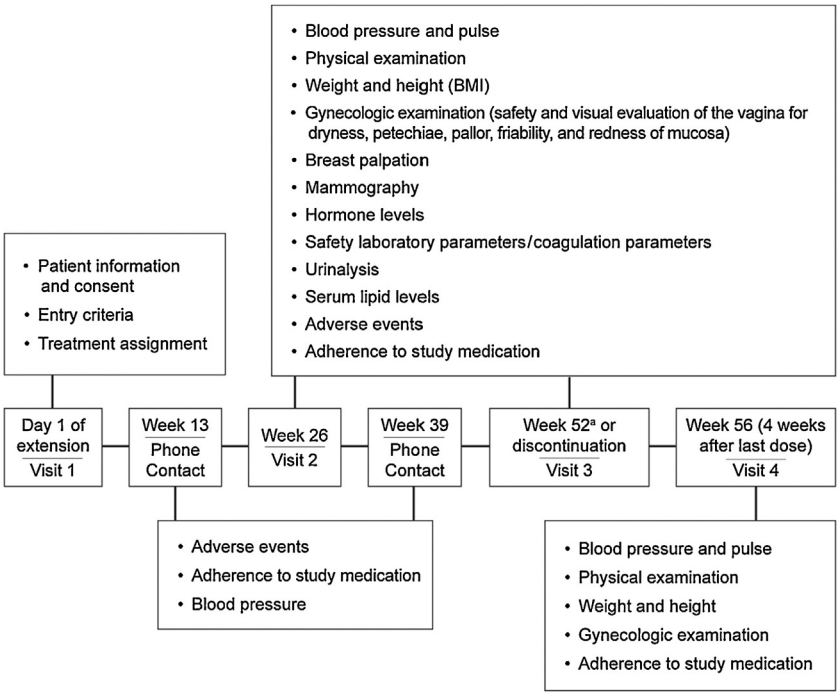

Fig. 2. Summary of assessments. [a]Papanicolaou smear was performed on women with an intact cervix at Week 52. BMI, body mass index.

visits throughout the study period. All AEs reported during the study were considered TEAEs, defined as any unfavorable event (including laboratory value, symptom, or disease) associated with the study drug or any other medicinal product taken by the participant. Significant worsening in health status or existing diseases observed during physical examinations were also considered AEs. A treatment-emergent serious AE (TESAE) was defined as any untoward medical event that resulted in death, was life threatening, required inpatient hospitalization or prolonged an existing hospitalization, or resulted in persistent or significant disability and/or incapacity.

The clinical examinations used to evaluate safety included physical examination and vital signs, breast palpation and mammograms, and gynecologic examinations. During visual examination of the vagina, specific observations were made for vaginal dryness, petechiae, pallor, friability, and redness of the mucosa. Each of these vaginal assessments was rated on the following 4-point scale: 0, none; 1, mild; 2, moderate; and 3, severe. Key laboratory assessments included serum lipid levels, hormone levels, and coagulation parameters.

2.4. Statistical methods

The primary objective of this study was to assess the long-term safety of 60-mg/day doses of ospemifene in the treatment of VVA in postmenopausal women without a uterus. The analysis characterized changes from Baseline in safety parameters. (As noted earlier, Baseline in the extension study refers to Baseline in the initial 12-week study.) All analyses were performed using SAS® Release 8.2 (SAS Institute Inc, Cary, NC) and were conducted in the intent-to-treat (ITT) population, defined as all study participants who received at least 1 dose of study medication. Descriptive statistics were used unless otherwise noted. For continuous variables, data were summarized, including the mean, standard deviation (SD), median, and minimum and maximum values. Categorical variables were summarized, including frequencies and percentages.

Demographic and Baseline characteristics were summarized using all data available for each variable. The study parameters were summarized using observed cases (OC) and the last observation carried forward (LOCF) method for available data at Week 26 ± 6 weeks and at Week 52 ± 6 weeks. Subjects were excluded from summaries where data were missing for a given parameter. AEs were coded by the Medical Dictionary for Regulatory Activities (MedDRA) version 9.1 and tabulated by system organ class (SOC), preferred term (PT), relationship to study drug, and severity. The most frequently occurring AEs, serious AEs, and AEs leading to study drug discontinuation were also summarized by SOC and PT.

3. Results

3.1. Participant disposition and demographics

A total of 379 participants who completed the initial 12-week study had had a total hysterectomy and thus were eligible to enter the safety extension study. For this investigation, 301 women were enrolled and included in the ITT population. No details were collected on the 78 women who elected not to enroll. Of these 301 participants, 184 (61%) completed the final treatment period (Week 52) of the extension (Fig. 1A). Baseline demographics and characteristics of the ITT population are shown in Table 1. The majority

Table 1
Demographic and Baseline clinical characteristics of the intent-to-treat population.[a]

Characteristic	Ospemifene 60 mg/day ($N = 301$)
Age (years), mean (SD)	59.4 (6.7)
BMI (kg/m^2), mean (SD)	26.9 (4.4)
Race, *n* (%)	
White	278 (92.4)
Black or African American	11 (3.7)
Asian	6 (2.0)
American Indian/Alaskan Native	3 (1.0)
Other	3 (1.0)

BMI, body mass index; SD, standard deviation.
[a] Demographic information was derived from the initial study of safety and efficacy.

Table 2
Summary of TEAEs during the 52-week extension study.

Event, *n* (%)	Ospemifene 60 mg/day (*N* = 301)[a,b]
TEAE	220 (73.1)
Serious TEAE	13 (4.3)
Most frequent TEAEs[c]	
Sinusitis	24 (8.0)
Urinary tract infection	26 (8.6)
Hot flushes	31 (10.3)
TEAE leading to discontinuation	34 (11.3)

TEAE, treatment-emergent adverse event.
[a] Does not include TEAEs that were ongoing from the 12-week pivotal study.
[b] Includes participants in the intent-to-treat population.
[c] Occurred in ≥5% of patients in any prior treatment group.

of participants were white (92.4%), the mean age was 59 years (range, 41–80 years), and the mean BMI was 26.9 kg/m^2 (range, 17.4–38.0 kg/m^2).

Among the ITT population, the mean adherence rate to the study drug was 86.7% and the mean duration of treatment was 309.2 days. A total of 117 participants (38.9%) discontinued treatment, most commonly because of withdrawal of consent (13.2%), followed by an AE (12.3%) and lost to follow-up (5.6%) (Fig. 1A). See below reasons for discontinuation and refer to Table 2.

3.2. Safety and tolerability

3.2.1. Treatment-emergent adverse events

A summary of TEAEs that developed in the ITT population during the 52-week extension study is provided in Table 2. Of the 301 participants, 220 (73.1%) experienced at least 1 TEAE during the extension study. Most TEAEs were rated mild or moderate in severity, and the most frequently reported TEAEs were hot flushes, sinusitis, and urinary tract infection; among these, only hot flushes was study drug-related (Table 2).

A total of 19 TESAEs were experienced by 13 participants. Only 1 TESAE was considered by the investigators to be possibly related to the study drug: a non-ST-elevation myocardial infarction in a 60-year-old woman with pre-existing cardiac disease (requiring stent placement 2.5 years before study enrollment) and a long history of type 2 diabetes mellitus, hyperlipidemia, and hypertension. A TESAE of hemorrhagic stroke, reported in 1 participant who completed the 12-week study on the 30-mg dose of ospemifene and had entered the extension study, experienced the cerebrovascular accident after 21 days on the 60-mg dose. The participant, who was concomitantly receiving sumatriptan, recovered and the event was considered by the investigator as unlikely related to ospemifene. Thirty-four participants discontinued treatment due to a TEAE that was not ongoing from the initial 12-week study. TEAEs that led to discontinuation in ≥2 participants included hot flushes (n = 6), nausea (n = 3), headache (n = 3), muscle spasms (n = 2), hyperhidrosis (n = 2), and rash (n = 2). All 6 participants who discontinued due to hot flushes had entered the initial 12-week study with hot flushes at Baseline. There was 1 case of superficial thrombophlebitis that resolved after 1 day of heparin treatment, but there were no cases of deep venous thromboembolism. There were no occurrences of pelvic organ prolapse, incontinence, fractures, breast cancer, and no deaths.

3.2.2. Clinical laboratory evaluations

No clinically significant changes occurred from Baseline to Week 26 or Week 52 in the levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Mean (±SD) total cholesterol declined from 213.2 (±38.2) mg/dL at Baseline to 208.3 (±32.8) mg/dL at Week 52; mean LDL cholesterol declined from 121.7 (±31.6) mg/dL to 116.1 (±27.0) mg/dL; and mean HDL cholesterol was virtually unchanged, increasing slightly from 63.4 (±15.6) mg/dL to 63.8 (±16.7) mg/dL. Mean triglycerides increased from 130.3 (±76.8) mg/dL to 135.5 (±65.3) mg/dL. A minor decrease in the mean fibrinogen levels and a minor increase in the mean protein-S antigen levels were observed at Weeks 26 and 52. Overall, the mean levels of other coagulation parameters remained essentially unchanged, and no AEs were reportedly related to coagulation parameters.

Table 3
Visual examination of the vagina in observed cases (OC)[a].

Parameter, mean (±SD)	Ospemifene 60 mg/day	
	Overall mean change from BL (initial study) to Week 26 (extension study) (*N* = 243)	Overall mean change from BL (initial study) to Week 52 (extension study) (*N* = 198)
Vaginal dryness in mucosa	−1.4 (±0.87)	−1.5 (±0.88)
Petechiae	−0.6 (±0.86)	−0.6 (±0.90)
Pallor	−1.0 (±0.95)	−1.2 (±0.95)
Friability	−0.8 (±0.89)	−0.8 (±0.91)
Vaginal redness in mucosa	−0.6 (±0.92)	−0.8 (±0.89)

BL, Baseline; SD, standard deviation.
Each characteristic was assessed on a 4-point scale: 0, none; 1, mild; 2, moderate; and 3, severe.
[a] Data collected from participants who discontinued the trial within 6 weeks of the final treatment visit (Week 52) were included in the OC analysis.

No clinically meaningful changes from Baseline in mean chemistry values were apparent at Week 26 or Week 52 using OC or LOCF methodology. Among OC, the levels of FSH and luteinizing hormone (LH) had decreased by Week 26 and Week 52, whereas sex hormone-binding globulin (SHBG) and total testosterone had increased, similar to the patterns of change observed in the initial 12-week study. The mean (±SD) changes from Baseline to Week 52 in FSH, LH, SHBG, and total testosterone were −15.9 (±13.6), −1.7 (±6.7), 72.7 (±39.1), and 2.2 (±5.2), respectively. No major changes were observed in mean estradiol (E2) or free testosterone values; the majority of E2 values were below the limit of detection (10 mg/mL).

3.2.3. Clinical signs and symptoms

No clinically significant changes were observed in the mean changes in vital signs at Weeks 26 or 52 of the extension study. There were a total of 9 TEAEs categorized as being related to the breast; however, only 4 were considered truly breast related, all of which were considered mild or moderate in severity. One patient in the ospemifene group had a breast-related TEAE (breast mass) that was ongoing at the end of the study and at the 4-week follow-up (Visit 4). Further follow-up of this patient found that results by mammography, conducted as part of routine care during the 5 years after study termination, were reported as normal. This AE was assessed as mild and unlikely related to the study drug.

Efficacy was assessed by visual examination of the vagina and showed improvements from Baseline in the mean severity scores for all 5 parameters (vaginal dryness, petechiae, pallor, friability, and redness of the mucosa) at Weeks 26 and 52 of the extension study (Table 3). Among participants assessed at Week 52, ≥93% had scores of 0 (“none”) or 1 (“mild”) for all visual examination parameters: vaginal dryness (93%), petechiae (96.5%), pallor (93%), friability (97%), and redness of the mucosa (96%), with the greatest percentage improvement from Baseline in number of patients scored as having “none” or “mild” for dryness by Week 52 (29.3% vs. 93.0%, respectively) (Fig. 3).

The percentage of patients assessed as “severe” (score = 3) at Baseline was 22.3% for vaginal dryness, 3.3% for petechiae, 13.3%

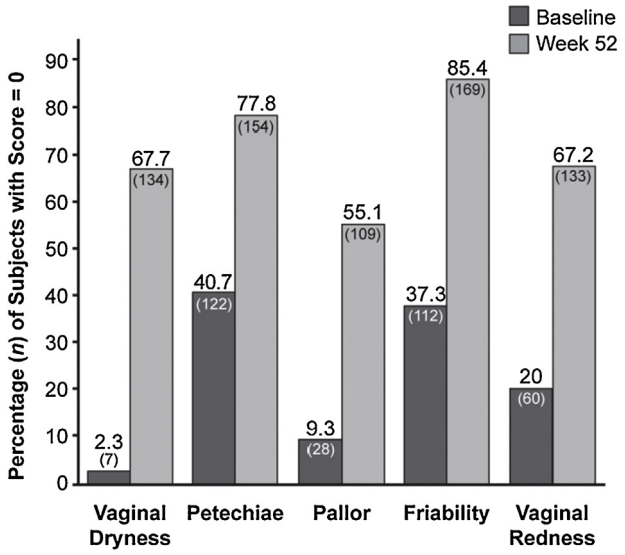

Fig. 3. Visual evaluation of the vagina. Percentage of participants with a score of 0 ("none") for each parameter, as assessed by visual evaluation of the vagina at Baseline and at Week 52 (observed cases). Data collected from subjects who discontinued the trial within 6 weeks of the final treatment visit (Week 52) were included in the observed cases analysis. Examination scoring scale: 0, none; 1, mild; 2, moderate; and 3, severe. (Baseline: *N* = 300 patients on ospemifene 60 mg/day; Week 52: *N* = 198 patients on ospemifene 60 mg/day.). The number in parentheses denotes the number of subjects.

for pallor, 4.7% for friability, and 4.7% for redness of the mucosa; at Week 52, the percentages were <0.5% for all parameters. Likewise, the percentage of patients assessed as "none" (score = 0) increased substantially between Baseline and Week 52 for all 5 parameters assessed by visual examination of the vagina.

4. Discussion

In this safety extension study of postmenopausal women with moderate to severe VVA who had previously undergone a hysterectomy, ospemifene 60 mg/day for up to 64 weeks was generally well tolerated. Consistent with previous studies, most AEs were mild or moderate in severity [20,21,23]. Although hot flushes were among the most common TEAEs in the extension study (observed in 10% of women), they were associated with a low rate of discontinuation (2%) and were experienced in participants with hot flushes upon entry into the initial 12-week study. Similar to findings in the 12-week study and the long-term follow-up of women with an intact uterus, there were no clinically significant adverse changes in lipids, coagulation parameters, or hormone levels among the women with no uterus [20,21]. Any breast-related TEAEs were considered mild or moderate in severity. The breast mass resolved in the ospemifene recipient whose mass was present through the 4-week follow-up period. Results of mammograms conducted as part of routine care visits after conclusion of the study were normal.

The effect of SERMs on pelvic organs is not class specific and each specific compound has different effects on the genitourinary tract. SERMs interact with both estrogen receptors α and β which are found throughout the urogenital tissue, including the urethra, levator ani, and anterior vaginal wall, as well as in the uterosacral ligaments [26–28]. The antagonistic effects of some SERMs may impact the continence mechanism and pelvic support. Development of levomeloxifene for treatment and prevention of osteoporosis was halted based on high incidence of adverse effects including a 7% vs. 2% incidence of prolapse over placebo and 17% vs. 4% incidence of incontinence over placebo [25]. Likewise, development of idoxifene was halted after preliminary observation indicated an increase of prolapse cases [24,29,30]. Raloxifene and tamoxifen may have an effect on prolapse or urinary incontinence but mixed results are reported [31]. The impact of SERMs on the pelvic floor and other urogenital tissue is important, particularly for women with hysterectomy given that hysterectomy may increase the risk for prolapse and incontinence [32,33]. In this 52-week extension study, no increased incidences of prolapse or incontinence were observed in hysterectomized women while taking ospemifene.

Ospemifene has demonstrated a unique tissue-selective activity profile suitable for its indicated use in postmenopausal women with VVA. Although the current study focused on safety, visual evaluations of the vagina showed sustained clinical improvements (e.g., a 2-level change, from "severe" to "none," "severe" to "mild," or "moderate" to "none") from Baseline in all 5 characteristics examined. Similarly, a greater percentage of patients at Week 52 compared to Baseline were assessed as having no finding of vaginal dryness (67.7% vs. 2.3%), petechiae (77.8% vs. 40.7%), pallor (55.1% vs. 9.3%), friability (85.4% vs. 37.3%), or redness of the mucosa (67.2% vs. 20.0%), respectively. The clinical observations in the present trial are consistent with results of the initial 12-week study and another long-term safety study and further demonstrate pelvic floor safety and a restoration of tissue quality and integrity in ospemifene-treated hysterectomized patients for up to 52 weeks [20,21]. The open-label design of the current trial could be considered a limitation of the study results.

5. Conclusions

Once-daily treatment with ospemifene 60 mg was effective and generally well tolerated in this long-term follow-up study of postmenopausal women without a uterus. Safety findings from this study are consistent with those of other Phase 3 studies in women with an intact uterus. Most AEs were generally considered to be mild to moderate in severity. Visual evaluations of the vagina showed sustained clinical improvement for all parameters throughout the 52-week extension study with a greater percentage of patients assessed as having no symptoms compared with Baseline. Additionally, no incidents of prolapse or incontinence TEAEs were observed for this group of hysterectomized women. Ospemifene, an estrogen agonist/antagonist with tissue-selective effects, is the first non-estrogen oral therapy suitable for its indicated use in the treatment of moderate to severe dyspareunia, a symptom of VVA. At the 60-mg dose for 52–64 weeks, ospemifene was safe and clinically effective in improving the symptoms of vaginal dryness and dyspareunia associated with VVA for women without a uterus.

Contributors

James Simon, MD, CCD, NCMP, FACOG: I declare that I participated in the content, material, writing, and editing, and that I have seen and approved the final version. I have the following conflicts of interest: served (within the last year) or is currently serving as a consultant to or on the advisory boards of: Abbott Laboratories/AbbVie, Inc. (North Chicago, IL), Agile Therapeutics, Inc. (Princeton, NJ), Amgen Inc. (Thousand Oaks, CA), Apotex, Inc. (Toronto, Canada), Ascend Therapeutics (Herndon, VA), BioSante (Lincolnshire, IL), Depomed, Inc. (Menlo Park, CA), Everett Laboratories, Inc. (West Orange, NJ), Intimina by Lelo, Inc. (San Jose. CA), Lupin Pharmaceuticals (Baltimore, MD), TherapeuticsMD (Boca Raton, FL), Meda Pharmaceuticals Inc. (Somerset, NJ), Merck & Co., Inc. (Whitehouse Station, NJ), Novartis Pharmaceuticals Corporation (East Hanover, NJ), Noven Pharmaceuticals, Inc. (New York, NY), Novo Nordisk (Bagsvrerd, Denmark),

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Competing interest

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Ethical approval

Institutional Review Board (IRB) approval was obtained for each study site, with a central IRB responsible for the initial and continuing review and approval of the clinical study and for complying with the requirements of section 21 of the Code of Federal Regulations (CFR), Part 56. The study was conducted in accordance with the guidelines of Good Clinical Practice, the Declaration of Helsinki, and all applicable local regulations. This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and current Good Clinical Practices and in compliance with local regulatory requirements and 21 CFR 312.

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