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Ospemifene for the treatment of menopausal vaginal dryness, a symptom of the genitourinary syndrome of menopause

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ABSTRACT

Introduction: Vulvovaginal atrophy (VVA), a component of the genitourinary syndrome of menopause, is a progressive condition due to decline in estrogen leading to vaginal and vulvar epithelial changes. Accompanying symptoms of dryness, irritation, burning, dysuria, and/or dyspareunia have a negative impact on quality of life. Ospemifene is a selective estrogen receptor modulator (SERM) approved by the FDA for moderate to severe dyspareunia and vaginal dryness due to postmenopausal VVA.

Areas covered: PubMed was searched from inception to March 2019 with keywords ospemifene and vulvar vaginal atrophy to review preclinical and clinical data describing the safety and efficacy of ospemifene for vaginal dryness and dyspareunia due to VVA. Covered topics include efficacy of ospemifene on vaginal cell populations, vaginal pH, and most bothersome VVA symptoms; imaging studies of vulvar and vaginal tissues; effects on sexual function; and safety of ospemifene on endometrium, cardiovascular system, and breast.

Expert opinion: Ospemifene is significantly more effective than placebo in all efficacy analyses studied, working through estrogen receptors and possibly androgen receptors. Safety as assessed by adverse events was generally comparable to that with placebo and to other SERMs, and/or adverse events were not clinically meaningful. No cases of endometrial or breast cancer were reported.

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1. Introduction

Estrogen levels at menopause decline by up to 90% [1], which leads to well-known adverse effects for many women. In addition to vasomotor symptoms (VMS; hot flashes), symptoms can include vulvovaginal atrophy (VVA), associated with thinning and drying of the vaginal epithelium and in turn leading to vulvar and vaginal dryness, irritation, burning, dysuria, dyspareunia, and discharge [2–4]. Estimates indicate that up to 45–50% of postmenopausal women experience VVA symptoms [5,6], and in US and international surveys of women with VVA symptoms, 50–60% rated their symptoms as moderate to severe [7–10]. In contrast to VMS due to menopause, VVA is likely to be progressive without intervention [2]. The decline in estrogen also affects the urinary tract, predisposing to frequency, urgency, nocturia, dysuria, and increased risk of urinary tract infections (UTIs); these effects together with symptomatic VVA are now termed the ‘genitourinary syndrome of menopause’ (GSM) [11].

VVA has a significant impact on women’s quality of life, including sexual activity and intimacy with their partners [2,3,6,8,9,12–14]. Most recently, severe vulvar and vaginal symptoms were shown to negatively affect sexual functioning scores in women of the European Vulvovaginal Epidemiology Survey (EVES) [12]. The Women’s EMPOWER survey found that 44% of women would like to have more sexual activity but didn’t because of their vaginal dryness/itching or dyspareunia, or if satisfied with their sexual activity level, would like it to be

more enjoyable or frequent by reducing or eliminating their symptoms [7]. Among 3046 postmenopausal women with VVA surveyed in REVIVE (Real Women’s Views of Treatment Options for Menopausal Vaginal Changes), 85% reported loss of intimacy, while about 25% reported declines in sleep, mood, and enjoyment of life [15]. Both men and women avoided intimacy with each other and had less sex because of the woman’s VVA, and these effects on one’s sex life were found to reduce self-esteem in a survey of 8200 European women and their male partners in the CLOSER survey (Clarifying Vaginal Atrophy’s Impact on Sex and Relationships) [13]. Effects on sexuality typically worsen over time, even with treatment [16].

Several studies show that dryness is the dominant symptom of VVA. In the multicenter AGATA study (Atrophy of the Vagina in Woman in Post-Menopause in Italy) of postmenopausal women recruited from outpatient gynecological services (n = 913), 82% reported vaginal dryness with 54% reporting vaginal dryness as their most bothersome symptom (MBS) [17]. Vaginal dryness was also the most prevalent symptom of women with VVA in reports of surveys globally [7–9,12].

1.1. Undertreatment of VVA and treatment need

While VMS improve over time, typically lasting 5–10 years [18,19] even without treatment, VVA is known to progress in the absence of intervention [2]. More than half of women with

Article Highlights

- Ospemifene is approved for the treatment of moderate to severe dyspareunia and/or vaginal dryness as a symptom of VVA due to menopause (in the US) and of moderate to severe symptomatic VVA in postmenopausal women not candidates for local vaginal estrogen therapy (in Europe)
- Objective and subjective measures, including vulvar-vestibular photography, show improvements in vaginal dryness and overall vulvar and vaginal health in postmenopausal women
- Safety (assessed by adverse events) was generally comparable to that with placebo and other SERMs
- No cases of endometrial or breast cancer were reported
- Longer-term data on the use of ospemifene will help create a better understanding of the best way to counsel women on using ospemifene as a VVA/GSM treatment

symptomatic VVA rate their symptoms as moderate to severe, but many fail to seek treatment [8,9,12,15,20,21]. Surveys found reasons for not seeking treatment include a belief that VVA is just something to live with, discomfort or embarrassment with the topic, lack of knowledge about treatment options, or dissatisfaction with current options [7,15,21].

Undertreatment of VVA may be related to women's not addressing the issue with their healthcare professionals. In the Vaginal Health: Insights, Views & Attitudes (VIVA) survey (n = 3520), 62% of women with VVA had consulted a health care professional, but 40% of this group waited ≥ 1 year to do so [8]. More than half (56%) of the surveyed women in the Women's EMPOWER study never discussed their vaginal symptoms with their healthcare professionals [7], and similarly in the REVIVE survey, 56% of women discussed VVA with a physician, but only 9% reported that their symptoms were specifically diagnosed as VVA [15]. In both of these surveys, only 7% of women used prescription therapies for VVA treatment [7,15].

1.2. Pathophysiology of VVA

Estrogen levels decline with age and the onset of menopause resulting in overt clinical and cellular changes in vaginal and vulvar tissues [2]. The vaginal epithelium is thinner, less elastic, pale, and dry, while the vagina and introitus may shorten and narrow [2,4]. Vaginal blood flow and natural secretions diminish, including lubrication during sexual activity, and inflammation (upon vaginal examination) may lead to a pathologic diagnosis of atrophic vaginitis [2,4]. Cytologic examination shows an evolution in vaginal epithelial cell types, from predominantly intermediate and superficial cells, with few parabasal cells (premenopause), to primarily parabasal cells and few superficial cells (postmenopause) [2]. Premenopausal women have a healthful population of vaginal lactobacilli, which maintain a strong epithelial barrier and a pH of 3.8 to 4.5, preventing urogenital infections [2]. However, during menopause, the change in vaginal cell populations reduces lactic acid generation from glycogen breakdown leading to rising pH, loss of lactobacilli, and overgrowth of other bacteria [22]. These consistent pathophysiologic findings have resulted in VVA diagnoses utilizing objective measures: a vaginal pH of ≥ 4.6 and $< 5\%$ superficial cells [22].

1.3. Current treatment options

Current treatment options for VVA include systemic hormone therapy (HT), vaginal estrogen compounds (creams, rings, tablets), and nonestrogen therapies including oral ospemifene, intravaginal dehydroepiandrosterone, and over-the-counter (OTC) lubricants and moisturizers [3,4]. The risks associated with longer-term systemic HT may limit their use for treating VVA unless VMS are also present [3,4]. Accordingly, local rather than systemic estrogens are recommended for treating isolated VVA symptoms, with vaginal estrogens to be given at the lowest dose and frequency possible to achieve a therapeutic effect [2,3]. However, many women are concerned about safety with estrogens given the early termination of the Women's Health Initiative (WHI) [23] and the boxed warning on both systemic HT and low-dose vaginal estrogens, even though experts argue that given its much lower systemic absorption, low-dose vaginal estrogens are unlikely to pose the same risks as systemic HT [3,24,25]. Nonhormonal options such as vaginal moisturizers provide temporary relief and may decrease vaginal pH, but cannot address the underlying pathophysiology [2]. Women in various studies have reported dissatisfaction with vaginal OTC products and prescription therapies because of inadequate symptom relief, messiness, inconvenience (eg, need for an applicator), burning, discharge, and concerns about hormone safety [7,15,16,26]. All of these issues can negatively affect treatment compliance [7,15,26].

1.4. Selective estrogen receptor modulators and ospemifene overview

Estrogen therapies have differential effects on body tissues, with a beneficial action on vaginal tissues and bone [27] but potential adverse effects on the endometrium (estrogen alone), as well as the cardiovascular system and breast (estrogen plus progestin) [3,23,28,29]. Selective estrogen receptor modulators (SERMs), also known as selective estrogen receptor agonist/antagonists (ERAs), have varying effects on target tissues depending on binding and activation of intracellular estrogen receptor (ER)- α , ER- β , or both, which function as ligand-inducible transcription factors regulating gene expression (as reviewed by [30]). Physiologic effects may manifest as estrogen agonist, antagonist, or neutral biologic effects depending on the specific SERM and dosage, ER subtype, tissue type, structure of the ligand-receptor complex, and involvement of transcriptional coactivators and corepressors [30].

Ospemifene is the only oral ERA (Figure 1) currently approved by the Food and Drug Administration (FDA) for the treatment of moderate to severe dyspareunia as a symptom of VVA due to menopause (approved in 2013) [31] and was recently approved for the treatment of moderate to severe vaginal dryness as a symptom of VVA due to menopause (January 2019) [31]. Ospemifene is also approved in the European Union for the treatment of moderate to severe symptomatic VVA in postmenopausal women who are not candidates for local vaginal estrogen therapy [32].

Ospemifene binds with approximately equal affinity to ER- α and ER- β [33] and differs from other SERMs (eg, tamoxifen, raloxifene, bazedoxifene) in its effects on target tissues [30].

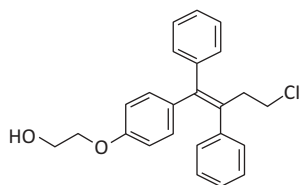


Figure 1. Chemical structure of ospemifene.

Preclinical data indicated that ospemifene acts as an ER agonist in the vagina and partial agonist in the uterus [33] and as an ER agonist in bone [34,35], while having a neutral to antagonistic effect in the breast [36,37]. Phase 3 clinical data confirm that ospemifene acts as a selective ER agonist on the vulva and vagina [38–41].

This article reviews the effects of ospemifene on symptoms of VVA with a focus on vaginal dryness.

2. Preclinical data

2.1. Vagina and uterus

Studies in ovariectomized rats demonstrated that ospemifene has partial ER agonist activity in the vagina and uterus. For example, ospemifene 10 mg/kg/day for 2 weeks increased vaginal weight and epithelial cell height, similar to the response observed with active control, 17- α ethinyl estradiol (EE; 0.1 mg/kg/day), for epithelial cell height and reaching 86% of the EE response for vaginal weight [33]. Effects with ospemifene were significantly greater than with vehicle but not significantly different from EE [33]. Histologic analysis confirmed increased thickness and mucification in the vaginal luminal epithelial area following ospemifene administration. Uterine weight also increased with ospemifene equivalent to 37% of the response seen with EE [33].

2.2. Breast

Ospemifene demonstrated anti-estrogenic effects in an in vitro model of estrogen-sensitive human breast adenocarcinoma cells (MCF-7 cells) [33]. Adding ospemifene to estrogen-dependent MCF-7 cells yielded no significant increase in cell growth in one study [34] and inhibited growth in another [37]. Ospemifene also significantly inhibited MCF-7 tumor growth relative to controls in ovariectomized mice [37], and inhibited the appearance of dimethylbenzanthracene (DMBA)-induced mammary tumors in DMBA-treated rats [34]. In another mouse tumor model (MTag 34 cell line), ospemifene inhibited the development and growth of ER-positive mammary tumors in vivo and prolonged survival times [42].

Unlike estradiol, but similar to the effects of raloxifene and tamoxifen, ospemifene was not associated with cell proliferation in mammary glands of ovariectomized rats [36]. Ospemifene inhibited human breast tissue cell proliferation in a dose-dependent manner compared with estradiol, based on decreased Ki-67 expression in tissue cultures of normal human mammary gland explants [43].

Breast tissue cultures from 26 postmenopausal women (ages 48–66 years) undergoing mastoplasty were treated with

ospemifene, raloxifene, tamoxifen, or estradiol for 7 to 14 days [44]. Ospemifene inhibited epithelial cell proliferation in a concentration- and time-dependent manner (at 100 nM on day 14, $p < 0.01$) and opposed the proliferative effects of estradiol ($p < 0.001$) [44]. These effects of ospemifene were similar to those of established SERMs, though generally requiring a higher dose and treatment duration. Estradiol inhibited epithelial cell apoptosis at both 7 and 14 days, while all of the SERMs had similar estrogenic agonist effects at day 7 (or at low doses) but antagonist effects at day 14 and at higher doses (100 nM), resulting in increased apoptosis ($p < 0.01$) [44].

Estrogen receptor- α , androgen receptor (AR), and AR-regulated apolipoprotein D (Apo-D) showed the same pattern of responses. All SERMs at 100 nM antagonized the estradiol-induced increase in the number of ER- α positive cells ($p < 0.001$) [44]. Whereas estradiol significantly decreased AR-expressing cells ($p < 0.001$), ospemifene and the other SERMs at 100 nM (but not at 1 nM) maintained AR-positive cells at control levels [44]. Likewise, the SERMs at concentrations of 100 nM opposed the estradiol-induced decrease in the number of Apo-D positive cells, although the increase in cell numbers with the SERMs was not significant. The SERMs in general had ER-agonist effects at 1 nM but ER-antagonist effects at 100 nM [44]. These results suggest that ospemifene counters estradiol and ER-mediated effects but maintains the functionality and availability of the AR and its associated effects in breast tissue [44].

2.3. Bone

Ospemifene administration in ovariectomized rats demonstrated an ER agonist effect on bone. Four weeks of ospemifene at 10 mg/kg prevented the loss of bone strength associated with ovariectomy [34]. Varying doses (1, 5, or 25 mg/kg) of ospemifene over 51 weeks prevented loss of bone mineral content (BMC) in the proximal femur, prevented BMC loss in the distal femur in a dose-dependent manner, and achieved significantly higher trabecular bone mineral density than in control animals [35]. Ospemifene normalized bone turnover rates in ovariectomized rats, inhibited the increase in osteoclasts and other bone resorption parameters, and decreased the percentage of eroded surface area [34,35].

3. Clinical efficacy data

3.1. Co-primary endpoints

3.1.1. Study methods

Several randomized phase 3 trials have characterized the effects of ospemifene on the vagina and endometrium (Table 1) [38–41,45–47]. Ospemifene efficacy and safety were evaluated in three 12-week randomized, double-blind, parallel-group, placebo-controlled studies including dosages of 30 and 60 mg/day (Bachmann et al; NCT00276094 [38]) and 60 mg/day (Portman et al, NCT00729469 [39,40] and Archer et al, NCT02638337 [41]), a 40-week extension study of long-term safety (Simon et al 2013, NCT01585558 [46]), a 52-week extension study of safety and efficacy (Simon et al 2014, NCT01586364 [45]), and an independent 52-week safety study (Goldstein et al, NCT00566982 [47]).

Table 1. Co-primary efficacy endpoints, phase 3 trials in ITT populations.

Study number Reference (Treatment Length)	Change from Baseline to Week 12				
	Study treatment (n)	% Superficial cells	% Parabasal cells	Vaginal pH	MBS severity score
NCT00276094 Bachmann et al 2010 [38] (12-week)	OSP 60 mg (276), OSP 30 mg (282), placebo (268)	10.8%, 7.8%, 2.2%; p < 0.001*	-30.1%, -21.9%, +3.98%; p < 0.001*	-1.01, -0.67, -0.10; p < 0.001*	Vaginal dryness: -1.26, -1.22, -0.84; p = 0.02, 60 mg vs placebo; p = 0.04, 30 mg vs placebo. Dyspareunia: -1.19, -1.02, -0.89; p = 0.023, 60 mg vs placebo; NS, 30 mg vs placebo NA
NCT01585558 Simon et al 2013 [46] (40-week extension)	OSP 60 mg (69), OSP 30 mg (62), placebo (49)	NA	NA	NA	NA
NCT01586364 Simon et al 2014 [45] (52-week extension)	OSP 60 mg (166), OSP 30 mg (159), placebo (156)	NA	NA	NA	NA
NCT00729469 Portman et al 2013 [39] (12-week)	Dyspareunia: OSP 60 mg (303), placebo (302)	12.3%, 1.7%; p < 0.0001	-40.2%, 0.0%; p < 0.0001	-0.94, -0.07; p < 0.0001	Dyspareunia: -1.5, -1.2; p = 0.0001
Portman et al 2014 [40]	Vaginal dryness: OSP 60 mg (160), placebo (154)	7.0%, 0%; p < 0.001†	-31.7%, -3.9%; p < 0.001	-0.95, -0.25; p < 0.001	Vaginal dryness: ITT: -1.3, -1.1; p = 0.080 (NS) (PP: -1.4, -1.1; p = 0.014) NA
NCT00566982 Goldstein et al 2014 [47] (52-week)	OSP 60 mg (363), placebo (63)	5.0%, 0%; p < 0.0001†	-40%, -0%; p < 0.0001†	-1.21, -0.16; p < 0.0001	NA
NCT02638337 Archer et al 2019 [41] (12-week)	OSP 60 mg (316), placebo (315)	7.8%, 0.6%; p < 0.0001	-23.7%, -1.9%; p < 0.0001	-1.01, -0.29; p < 0.0001	Vaginal dryness: -1.29, -0.91 p < 0.0001

ITT: intent to treat; MBS: most bothersome symptom; NA: not assessed; NS: not significant; PP: per protocol; OSP: ospemifene.

All trials were randomized, double-blind, parallel-group, phase 3 studies. Participants in all studies were postmenopausal women with VVA. All outcomes reflect change from BL to week 12; data are means unless otherwise indicated. P values compare change from baseline for ospemifene vs placebo; *for each ospemifene dose group vs placebo; †medians.

Women were eligible for the three 12-week trials if they had $\leq 5\%$ superficial cells on vaginal smear (ie, vaginal maturation index; VMI), vaginal pH > 5.0 , and at least one moderate to severe VVA symptom considered to be their MBS [38–41]. The 12-week trials all assessed 4 co-primary endpoints: change from baseline to week 12 in the proportion of superficial cells and parabasal cells on vaginal smear, vaginal pH, and severity of the MBS, defined as either vaginal dryness or dyspareunia and rated 0–3, from none to severe [38–41]. The extension studies evaluated safety data at 40 weeks in women with a uterus [46] and 52 weeks in women without a uterus [45]. The independent 52-week study examined safety and efficacy of ospemifene 60 mg/day in women with VVA and an intact uterus, with primary outcomes of changes in VMI (percentage of parabasal and superficial cells) and vaginal pH up to week 12, and secondary outcomes of visual appearance of the vagina, serum hormone levels, VMI, and pH up to week 52 [47].

Most of the phase 3 trials included white women (80%–90%) aged 58–60 years, with body mass index (BMI) of 25–27 kg/m² [38–41,45–47].

3.1.2. Study results

Collectively, the studies assessing VMI reported significant improvements from baseline to week 12 in women treated with ospemifene, with increases in the percentage of superficial cells (range, 5.0% to 12.3%) and decreases in parabasal cells (range, – 23.7% to – 40.2%) that were significantly different from placebo (all doses, $p < 0.001$; Table 1). Vaginal pH also declined (range, – 0.94 to – 1.21) over 12 weeks compared with placebo (all doses, $p < 0.001$) [38–41,47].

In the 12-week trial by Bachmann et al ($n = 826$), 46% of women reported their MBS to be dyspareunia at baseline evaluation [38]. Symptom scores for dyspareunia declined significantly with 60 mg ospemifene compared with placebo ($p < 0.05$) [38]. Similarly, in the trial reported by Portman et al, which enrolled women with dyspareunia as the MBS at baseline, ospemifene 60 mg/day for 12 weeks significantly decreased dyspareunia scores ($p < 0.001$ vs placebo) [39].

In a VVA responder analysis [48] from 2 of the 12-week phase 3 trials [38–40], responders had a change from baseline in each of 3 criteria: a > 10 -unit increase in Maturation Value (percentage of superficial cells + [percentage of intermediate cells $\times 0.5$] + [percentage of parabasal cells $\times 0$]), a decrease of ≥ 0.5 in vaginal pH, and a decrease of ≥ 1 point in MBS severity score [48]. Percentages of responders were significantly higher for ospemifene 60 mg (33.7–39.7%) versus placebo (3.4–5.5%; $p < 0.001$ in both studies).

A pooled analysis of the 12-week phase 3 trials [38–40] assessed the clinical relevance of VVA improvement based on the 4-point severity scoring system (0–3, from none to severe) in 3 categories: improvement (reduction of ≥ 1 unit), substantial improvement (reduction of 2–3 units), and relief (final score of mild or none) [49]. Women with the MBS of dyspareunia had clinically relevant outcomes of improvement and relief at week 12 (both, $p \leq 0.03$ vs placebo) [50].

A recent meta-analysis of randomized controlled trials (RCTs) evaluating the 4 co-primary endpoints confirmed significant benefits of ospemifene after 12 weeks in the intent-to-treat

(ITT) population for vaginal pH (3 RCTs, $n = 1345$; standardized mean difference [SMD] – 0.96; $p < 0.0001$), vaginal parabasal cells (3 RCTs, $n = 1345$; SMD – 36.84; $p < 0.0001$), vaginal superficial cells (2 RCTs, $n = 1031$; SMD 8.23; $p < 0.0003$), and MBS of dyspareunia (1 RCT, SMD – 2.70; $p < 0.0001$) [51].

3.2. Vaginal dryness as MBS

Randomized, double-blind phase 3 trials have evaluated moderate to severe vaginal dryness as the MBS in women with VVA due to menopause. The 12-week clinical trial by Bachmann et al ($n = 826$) found 39% of women reported their MBS to be vaginal dryness at baseline [38]. Vaginal dryness symptom scores decreased significantly with ospemifene 60 mg compared with placebo ($p < 0.05$) by 12 weeks [38]. A clinical trial of 314 women with a baseline MBS of moderate to severe vaginal dryness found using ospemifene 60 mg/day for 12 weeks significantly improved the severity score for vaginal dryness in the per-protocol population ($p = 0.014$), but not in the ITT population [40].

The clinical relevance of ospemifene's effect on VVA symptoms was confirmed in another analysis of the 12-week phase 3 trials [38–40] in which significant percentages of women with an MBS of vaginal dryness experienced improvement, substantial improvement, and relief from baseline (all, $p \leq 0.05$ vs placebo) [50].

These results were confirmed in the most recent study of women with vaginal dryness as the MBS ($n = 631$) [41]. Women receiving ospemifene 60 mg/day had significant improvement in vaginal dryness compared with placebo at 12 weeks ($p < 0.0001$), and this improvement was evident by 4 weeks. Responder analysis showed a significantly higher rate of responders with ospemifene than with placebo at 12 weeks (31.5% vs 6.0%; $p < 0.0001$); the responder results were also significant by week 4 (19.2% vs 2.6%) [41].

3.3. Visual assessments and vulvar-vestibular imaging

Both visual assessment questionnaires and vulvar-vestibular imaging extend the subjective measure of improved vaginal dryness scores with ospemifene. Phase 3 trials assessed visual signs of VVA as a secondary outcome, using a 4-point scale (from 0 = no atrophy to 3 = severe atrophy) to evaluate vaginal dryness, petechiae, pallor, friability, and redness of the vaginal mucosa [39,47]. The 52-week follow-up study found that ospemifene significantly improved scores for all 5 measured parameters relative to placebo at weeks 12, 26, and 52 (all, $p < 0.0001$ vs baseline) [47]. Post hoc analysis of these phase 3 trials reported a significant increase from baseline in the proportions of women with no physical findings of atrophy (ie, score of 0 on all 5 measures) with ospemifene at weeks 12, 26, and 52 [52].

A recent single-arm, open-label pilot study used vulvoscopy to explore the effect of ospemifene for 20 weeks on vulvar and vaginal tissues of 8 postmenopausal women [53]. Women were aged 21–80 years (mean 59 years), with BMI < 37 kg/m², moderate to severe dyspareunia, and moderate to severe pain on cotton-tipped swab testing [53]. Photographs at baseline ($n = 118$) and end of study ($n = 140$) were examined with the Vulvoscopic Genital Tissue Appearance Scale (VGTAS; unvalidated 4-point scale), which

includes changes in 10 tissues (labia majora, labia minora, clitoris, urethral meatus, introitus, vestibular pallor, vestibular erythema, vestibular moisture, vaginal rugae, and anterior vaginal wall; maximum score 30) [53]. Total VGTAS score improved (decreased) significantly from baseline to week 20 (from 17.5 to 9.5; $p < 0.012$), as did 7 of 10 tissues (all, $p < 0.05$). Tissue improvements were also reflected in reduced pain score on cotton-tipped swab test (from 12.9 to 1.9; $p = 0.011$) and greater proportions of women reporting decreases in dryness and dyspareunia (both, $p < 0.02$) [53].

Another pilot study of 52 postmenopausal women with ≥ 1 moderate to severe symptom of VVA (vaginal dryness, burning, or dyspareunia) combined clinical photographs, visual examination of the vulvar vestibule (scored 0–3 each for petechiae, pallor, friability, dryness, and mucosal redness), cotton swab testing at 7 foci around the vestibule, and current perception threshold (CPT) testing for integrity of afferent nerve fibers at the vulvar vestibule [54]. All patients took ospemifene for 60 days, and all parameters improved significantly after treatment, including dryness, burning, dyspareunia, pain on cotton swab test, vulvar vestibular trophic score on visual exam, and CPT values (all, $p < 0.05$ vs baseline) [54].

A recent 12-week, randomized, double-blind, placebo-controlled phase 3 study (NCT02638337 [41]) reported the use of vulvar-vestibular photography and direct visual assessments as secondary outcomes in 631 postmenopausal women with moderate to severe vaginal dryness [55]. Women aged 40–80 years with vaginal dryness as their MBS, $\leq 5\%$ superficial cells in VMI, and vaginal pH > 5.0 took ospemifene or placebo

[55]. Tissue changes from baseline to 12 weeks were assessed with the Vulvar Imaging Assessment Scale (VIAS; unvalidated 4-point scale) including 9 criteria (labia majora, labia minora, clitoris size, introital tissue elasticity, introital color, introital erythema, introital moisture, urethral glans prominence, and other findings; maximum score 27) [55]. The Vaginal Health Index (VHI; unvalidated scale) assessed overall elasticity, fluid secretion, pH, condition of the epithelial mucosa, and moisture (each on a 5-point scale; maximum score 25), and the Vulvar Health Index (VuHI; unvalidated scale) assessed labia majora, labia minora, clitoris, introital tissue elasticity, color, discomfort and pain, and any other findings (each on a 4-point scale; maximum score 21) [55].

VIAS results showed significant improvements (decreases) from baseline to week 12 in vulvar-vestibular tissue appearance with ospemifene versus placebo (difference in least-square mean [LSM] change for total score, -1.0 ; $p = 0.015$) [55]. Both VHI and VuHI total scores also significantly improved (indicated by an increase and decrease, respectively) at week 12 (differences in LSM change: VHI, 2.8; VuHI, -1.2 ; both comparisons, $p < 0.0001$ vs placebo), and these changes were already apparent at week 4 [55]. Representative vulvar-vestibular photographs from before and prospectively after ospemifene treatment showed increased tissue in the labia minora, decreased erythema of the distal urethral meatus, lesser prominence of the distal urethra, decreased vestibular petechiae and pallor, and improvement of introital stenosis, compared with no improvements in the placebo group (Figure 2) [55]. More specifically for the labia minora, some women had a reversal of labia minora resorption and/or

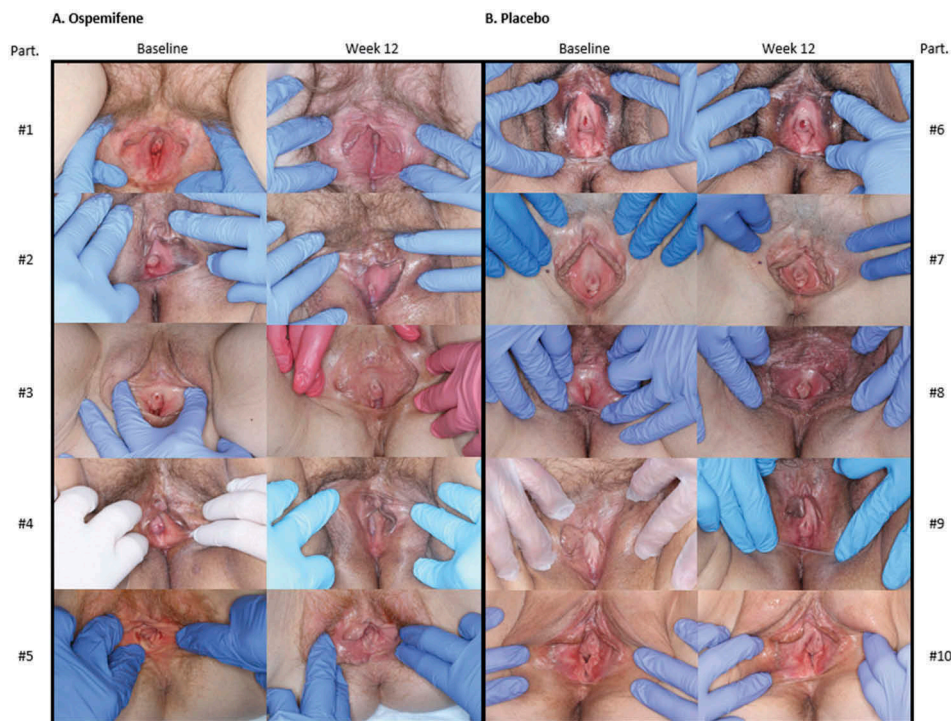


Figure 2. Representative vulvar and vestibular photographs for the Vulvar Imaging Assessment Scale (VIAS) of participants before and after ospemifene (on the left; A) and before and after placebo (on the right; B) for 12 weeks. Images from baseline to week 12 for participants randomized to ospemifene (A) show a greater amount of pink vestibular tissue with reduced pallor and reduced erythema, as well as less protrusion of the urethral glans tissue and less introital stenosis. Participant 1 also had an increase in the labia minora tissue. All images from baseline to week 12 of placebo-treated patients on the right (B) show no improvement or worsening of the vestibular pallor and erythema, protrusion of the urethral glans tissue, and introital stenosis; none had an increase in the labia minora tissue. Part., Participants. Reprinted with permission from Goldstein et al 2019 [55].

more robust labia minora tissue in terms of increased width and length with ospemifene, but women consistently had no improvements with placebo. Collectively, the results lend support to the use of vulvar-vestibular visual inspection and photography to assess VVA in postmenopausal women [55].

3.4. Histological studies

Recent histological studies in women with VVA provide direct evidence of the effects of ospemifene on vaginal tissues [56,57]. A histologic study assessed 32 healthy postmenopausal women aged 50–80 years, 16 taking ospemifene for ≥ 1 month and 16 untreated controls, who had vaginal biopsies at several sites during elective surgery [56]. Use of ospemifene 60 mg/day was associated with greater glycogen stores than in untreated women, as well as a thicker vaginal epithelial layer (349 vs 245 μm ; $p < 0.001$), higher proliferation index (212 vs 127 Ki-67 positive cells/mm; $p < 0.001$), and higher ER- α expression in both the epithelial (27.3 vs 20.6 points) and stromal layer (26.6 vs 20.6 points) of the vaginal wall (both, $p < 0.001$) [56].

A similar study included 11 ospemifene-treated and 9 untreated women, with vaginal and vulvar biopsies of ospemifene-treated women showing higher glycogen content, greater vaginal epithelial thickness (405 vs 252 μm ; $p = 0.001$) and vulvar epithelial thickness (311 vs 202 μm ; $p = 0.018$), higher vaginal proliferation index (170 vs 106 Ki-67 positive cells/mm; $p < 0.001$) and vestibular proliferation index (145 vs 99 Ki-67 positive cells/mm; $p = 0.007$), and a significant correlation between vaginal and vestibular proliferation index ($P = 0.003$). Treated women also had higher collagen content in both the vaginal ($p = 0.002$) and vulvar tissues ($p = 0.02$) and a higher collagen type I/III ratio in vaginal tissues ($p = 0.014$), although the increase in the ratio was not significant in vulvar tissues [57]. Results of the 2 studies confirm a beneficial effect of ospemifene on morphologic and physiologic features of vulvar as well as vaginal tissues [56,57].

3.5. FSFI improvement

A follow-up study to the phase 3, randomized, double-blind NCT00729469 trial [39] compared ospemifene versus placebo for the secondary outcome of change on the Female Sexual Function Index (FSFI; measuring domains of desire, arousal, lubrication, orgasm, satisfaction, and pain) [58]. Data were evaluated in the ITT population ($n = 919$) with last observation carried forward, and women were stratified by reported MBS of dyspareunia or vaginal dryness. Ospemifene was associated with significantly greater improvement in FSFI total score in the overall group and in the dyspareunia subgroup at weeks 4 and 12 (all, $p < 0.002$ vs placebo); improvements were also seen in the vaginal dryness subgroup at weeks 4 and 12, but the results were not statistically significant. FSFI total score significantly improved after 12 weeks of ospemifene versus placebo in women either with or without a uterus (both, $p \leq 0.01$ vs placebo). All FSFI domain scores (desire, arousal, lubrication, orgasm, satisfaction, and pain) significantly improved by week 12 with ospemifene versus placebo in the total ITT population and in the dyspareunia subgroup (all, $p < 0.05$ vs placebo), but

not in the vaginal dryness subgroup. At week 12, women with a uterus had significant improvements in all 6 domain scores, while women post-hysterectomy had improvements in 3 of 6 scores [58]. It should be noted that ospemifene is not approved for the treatment of female sexual dysfunction. The observed benefit may simply reflect improvements in vaginal health and reduction in severity of VVA, particularly in sexually active women with dyspareunia [58].

A study by De Rosa et al examined the effect of ospemifene on sexual function of women with VVA after treatment for cervical cancer [59]. Women ($n = 52$) aged 18–60 years who were 5 years post-treatment of stage I-IIa cervical cancer and were sexually active were enrolled in a single-arm prospective study of ospemifene 60 mg/day for 6 months. Outcomes were VHI (including vaginal moisture, fluid volume, elasticity, pH, and epithelial integrity scored from 1 [poorest] to 5 [best]) and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, which includes a Cervical Cancer Module with measures of sexual function. Total VHI score improved from a median of 10.0 at baseline to 16.0 at 6 months, and each individual component also improved over time (all, $p < 0.001$). Sexual activity, sexual vaginal functioning, and sexual enjoyment all improved, as did global health status and emotional and social functioning (all comparisons, $p \leq 0.01$ vs baseline) [59].

The 12-week confirmatory trial by Archer et al in 631 women with vaginal dryness as the MBS at enrollment found the FSFI total score to improve significantly with ospemifene versus placebo (5.7 vs 4.1; $p < 0.04$); significant improvements were also found in the domains of lubrication and pain [41]. Improved vulvar-vestibular tissue appearance observed by vulvar-vestibular photography and direct visual assessments in postmenopausal women with moderate to severe vaginal dryness was reflected in significant correlations of VHI and VuHI scores with both vaginal dryness severity and FSFI total scores in the same study (all, $p < 0.0001$) [55].

3.6. Lubricant use

Lubricant use in the 12-week phase 3 trials tended to decrease over time in both groups, but the decline was larger in the 60-mg ospemifene users versus placebo [38]. In trials in which lubricant was supplied to study participants for as-needed application, lubricant usage declined from 33.2% to 22.3% with ospemifene and from 34.0% to 29.4% with placebo [38,52]. Another trial reported greater declines, from 41.7% to 35.1% with ospemifene and from 43.1% to 39.3% with placebo [39]. Less need for lubricant presumably reflects improvements in physiologic and clinical parameters [52]. This is also reflected in the vulvar-vestibular photography reported by Goldstein and colleagues indicating no physiologic improvements with placebo and as-needed lubricant (Figure 2) [55].

A post hoc analysis of phase 3 trials [38,39,47] explored the effect of lubricant use on vaginal cell populations (proportion of superficial and parabasal cells), vaginal pH, and visual vaginal examination in women with VVA [52]. More ospemifene-treated women experienced complete resolution of all clinical signs of VVA at both 12 and 52 weeks, while the placebo patients had no improvement in VMI or vaginal pH regardless

of lubricant use, suggesting that nonhormonal lubricants do not influence VVA pathophysiology [52]. The frequency of lubricant use did not change with ospemifene or placebo throughout the most recent phase 3 study evaluating vaginal dryness and was similar between the treatment groups [41].

3.7. Pharmacokinetics and serum hormone levels

Several studies have clarified the pharmacokinetic (PK) characteristics of ospemifene and its effects on systemic hormones.

3.7.1. Pharmacokinetics

Kubota et al developed a population-based PK model using pooled ospemifene concentration data (total 3652 samples) from (primarily) phase 3 trials, repeated-dose phase 1 studies, and studies in special populations, including 997 postmenopausal women taking ospemifene 30 mg/day or 60 mg/day in the fed state [60]. Final population PK parameter estimates were 9.16 L/h for apparent total-body clearance, 34.3 L for apparent distribution volume in the central compartment, 16.4 L/h for apparent intercompartment clearance, 250 L for apparent distribution volume of the peripheral compartment, and 0.522/hour for absorption rate constant. Ospemifene PK parameters did not vary by age, race, body weight, BMI, albumin, alanine aminotransferase, bilirubin, or creatinine clearance, indicating that dose adjustments are not needed [60].

Ospemifene is metabolized mainly in the liver by cytochrome P450 enzymes, primarily excreted in the bile, and eliminated in the feces [60,61]. PK parameters are therefore not affected in patients with impaired renal function. Ospemifene may be used cautiously in patients with moderate hepatic impairment and with coadministration of ketoconazole; however, ospemifene should not be given with concomitant fluconazole [60,61].

An interspecies analysis of ospemifene revealed quantitative and qualitative differences in drug metabolism among species (analyzed in human, dog, rat, and monkey liver samples). However, in vitro findings were found to adequately predict in vivo phenomena, such that preclinical PK data can be applied to human patients for efficacy and toxicity analyses [62].

3.7.2. Serum hormones

A 12-week study of ospemifene 60 mg/day found slight decreases in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from baseline, and increases in sex hormone-binding globulin (SHBG), but all values remained well within the normal postmenopausal ranges [58]. There was also a slight increase in total serum testosterone but no change in free testosterone [58]. The 52-week safety study of ospemifene 60 mg/day, found levels of estradiol, LH, and FSH remaining within the normal postmenopausal ranges [47]. Levels of SHBG rose by 50% from baseline in the ospemifene group ($p < 0.0001$) but not with placebo ($p = 0.70$). The clinical significance of this difference is not known although this degree of increase in SHBG is similar to that of other SERMs and lower than that typically observed for oral HT [63].

4. Clinical safety data

4.1. Overall safety

4.1.1. Individual studies

Hot flushes were the most common treatment-emergent adverse event (TEAE) with ospemifene in study NCT00276094 (8.3% vs 3.4% with placebo) [38] and in study NCT00729469 for the MBS of dyspareunia (6.6% vs 4.3%) [39]. Hot flushes rarely led to treatment discontinuation, with withdrawal rates of 0.4% for NCT00276094 [38]; 0.33% and 1.87% for the dyspareunia [39] and vaginal dryness [40] subgroups, respectively, of NCT00729469; and ~2% for the extension studies [45–47] over 1 year. Likewise, hot flushes were the most common TEAE in the study of women with vaginal dryness as MBS (NCT02638337; 6.3% for ospemifene vs 2.6% for placebo) and were rarely a cause of study dropout (0.9% vs 0.1%) [41].

UTI was the most common TEAE among women receiving ospemifene in the subgroup with MBS of vaginal dryness in Portman et al (12.5% vs 7.8% with placebo) [40], but was not more common with ospemifene in the latest study of vaginal dryness (2.2% for ospemifene vs 3.2% for placebo) [41]. UTI ranked as the second most common TEAE by Bachmann et al (7.2% vs 2.2% with placebo) [38] and in the subgroup of women with MBS of dyspareunia by Portman et al (5.6% vs 3.6% with placebo) [39]. In contrast, the 52-week follow-up study found a lower rate of UTI with ospemifene than with placebo (16.8% vs 24.2%) [47]. The reasons for an increase in UTI incidence at 12 weeks followed by a decrease with long-term ospemifene use are unclear. A short-term increase in UTIs may be due to more frequent sexual activity, whereas during long-term use, the therapeutic effect would be expected to improve vaginal protective mechanisms, with lower vaginal pH, recolonization of lactobacilli, and decrease in coliforms, resulting in fewer UTIs [46].

Overall, study withdrawal due to adverse events (AEs) was uncommon; the highest reported per-study withdrawal rate due to AEs was 13.5% for ospemifene and 9.7% for placebo [47]. Few serious AEs were reported with either ospemifene or placebo (4.9% vs 6.5%, respectively) [47].

The population PK model developed by Kubota et al analyzed the risk of AEs by quartile of ospemifene exposure calculated as area under the curve [60]. For the 3 most frequent AEs, rates were similar between the highest and lowest exposure quartiles, including hot flush (13.4% vs 11.0%, respectively), nasopharyngitis (13.4% vs 11.0%), and headache (8.5% for both); therefore, serum exposure was not associated with safety parameters [60].

4.1.2. Pooled analyses and meta-analyses

A pooled post hoc analysis of randomized, double-blind phase 2/3 trials in postmenopausal women with or without VVA showed that when reported as TEAEs (5 placebo-controlled studies; $n = 2166$), hot flushes were significantly more prevalent in the ospemifene-treated group ($n = 1242$) than with placebo ($n = 924$) (8.5% vs 3.2%; $p < 0.0001$), but when hot flushes were evaluated as an efficacy endpoint in randomized clinical trials (3 studies), ospemifene did not worsen the frequency or severity of hot flushes versus placebo [64]. When

present, hot flushes were most frequent during the first 4 weeks of treatment and decreased over time. Independent predictors of worse hot flushes were recent HT before ospemifene treatment, higher baseline hot flush frequency, and longer treatment duration. Study discontinuation due to AEs was 7.6% with ospemifene and 3.7% with placebo [64].

Another pooled post hoc analysis of 6 phase 2/3 randomized, double-blind trials compared ospemifene 60 mg/day (treatment duration 6–52 weeks; median 86 days) versus placebo in 2200 postmenopausal women with various characteristics at enrollment (eg, $\leq 5\%$ vaginal superficial cells, vaginal pH > 5.0 , ≥ 1 MBS due to VVA, and/or hot flushes) [65]. While ospemifene was associated with more TEAEs than placebo (67.6% vs 54.1%) and more TEAE-related study discontinuations (7.6% vs 3.8%), most TEAEs were mild to moderate in severity and occurred within 4 to 12 weeks of treatment initiation [65]. The most common TEAEs occurring more frequently with ospemifene were hot flushes (8.5% vs 3.3%), UTI (6.5% vs 4.8%), and nasopharyngitis (5.4% vs 3.1%). Serious AEs were uncommon (2.6% vs 1.8%) and most were considered unrelated to treatment [65].

A meta-analysis of 6 RCTs published up to July 2018 compared ospemifene 60 mg/day versus placebo for side effects and safety [66]. Ospemifene was associated with a higher rate of hot flushes at 12 weeks (odds ratio [OR] 2.36; 95% confidence interval [CI], 1.26–4.42) but not at 52 weeks (OR 1.30; 95% CI, 0.40–4.25), and a higher incidence of UTI at 12 weeks (OR 1.97; 95% CI, 1.23–3.14) but not at 52 weeks (OR 0.70; 95% CI, 0.39–1.24) [66]. No significant differences were found for any of the other side effects studied, including headache, vaginal bleeding at 12 and 52 weeks, deep venous thrombosis (DVT), coronary heart disease, cardiovascular events, discontinuation due to AEs, and serious AEs [66].

4.2. Endometrium

Constantine et al performed a post hoc study for endometrial safety of ospemifene 60 mg/day from 5 trials [38–40,46,47] of postmenopausal women treated for up to 1 year [67]. A total of 1242 women received ospemifene (851 with an intact uterus) and 924 received placebo (543 with a uterus). Endometrial thickness increased by a mean of 0.81 versus 0.07 mm in the ospemifene and placebo groups, respectively, from baseline to 12 months ($p \leq 0.001$). Rates of vaginal bleeding or spotting among women with a uterus were not significantly different between groups (1.2% vs 0.9%; $p = 0.7$). No association was found between vaginal bleeding and endometrial thickness, and there were no reported cases of hyperplasia or endometrial cancer, suggesting that ospemifene is not a significant estrogen agonist for the endometrium [67].

Histologic analysis at 12 months showed that the endometrial pattern was similar to that at baseline in women receiving ospemifene (96.5%) and placebo (100%) [67]. Among women taking ospemifene, 2.0% had weakly proliferative endometrium, 0.3% had actively proliferative endometrium, 0.3% had a proliferative pattern, and 0.9% had various types of polyps [67]. Rates of suspected polyps did not differ between groups (1.4% with ospemifene; 1.6% with placebo) [67]. One woman from the ospemifene group had endometrial simple hyperplasia without atypia detected 3 months after the final dose; her

history included enoxaparin treatment for a fractured foot, which led to vaginal bleeding [47,67]. This incidence rate (0.3%) for endometrial hyperplasia is well below the rate of $\leq 1\%$ specified for postmenopausal women in the FDA guidance for VVA trials [47,67,68].

In the recent meta-analysis of 6 RCTs, endometrial thickness was significantly greater with ospemifene compared with placebo at 12 weeks (5 RCTs; SMD 0.40; 95% CI 0.17–0.63; $p < 0.0005$) and at 52 weeks (2 RCTs; SMD 0.62; 95% CI, 0.23–1.01; $p = 0.002$); however, the increase of < 1 mm was considered not clinically meaningful. There were no cases of endometrial cancer [66].

Collectively, these data indicate that up to 1 year of ospemifene treatment is safe for the endometrium. However, the ospemifene prescribing information still carries a boxed warning about an increased risk of endometrial cancer [31], which some authorities considered unwarranted [24,69].

For other reproductive tissues, no cases of cervical cancer or precancer or ovarian cysts were found in the phase 3 trials and extension studies [38–41,45–47].

4.3. Venous thromboembolism and cardiovascular disease

SERMs as a class have been shown to increase the risk of venous thromboembolism (VTE) by approximately 2-fold [70,71]. The 52-week safety study of women with VVA (294 taking ospemifene; 55 taking placebo) reported 2 cerebrovascular accidents with ospemifene, 1 of which was a nonfatal stroke considered possibly treatment related, and 1 case of DVT, also in a patient treated with ospemifene and also judged to be possibly treatment related [47]. One hemorrhagic stroke and one non-ST elevation myocardial infarction in the ospemifene group were reported in the 52-week extension study among women without a uterus [45]. No cases of VTE were reported in the 40- and 52-week extension studies [45,46].

The US FDA product label, based on the most recent comprehensive safety data (2019), reports incidences of cerebral thromboembolic and hemorrhagic stroke with ospemifene 60 mg of 1.13 and 3.39 per 1000 women-years, respectively, compared with 3.15 and 0 per 1000 with placebo, respectively [31]. The incidence rate for DVT with ospemifene 60 mg is 2.26 per 1000 women-years (2 reported cases) compared with 3.15 per 1000 women-years (1 reported case) with placebo [31]. These numbers are similar to the expected SERM class effect of an increased VTE risk [70,71] and thus, stroke and DVT are listed as risks in the boxed warning label for ospemifene in the US FDA label [31]. The European label, based on older comprehensive safety data (2015), reports an incidence of DVT of approximately 3.65 cases per 1,000 women-years (95% CI of 0.44 to 13.19) with 60 mg ospemifene versus 3.66 cases per 1,000 women-years (95% CI of 0.09 to 20.41; relative risk is 1.0) for placebo across all placebo-controlled studies [32].

A post hoc analysis of 5 randomized, double-blind, placebo-controlled phase 2/3 trials (study duration, 6 weeks to 12 months) evaluated cardiovascular disease surrogate markers of lipids and coagulation factors in postmenopausal women receiving ospemifene 60 mg/day ($n = 1242$) or placebo ($n = 924$) [72]. Ospemifene was associated with significant increases in high-density

lipoprotein cholesterol at 3, 6, and 12 months; decreases in low-density lipoprotein cholesterol at 3, 6, and 12 months; and a decrease in total cholesterol at 6 months (all, $p \leq 0.04$ vs placebo) [72]. Increases in triglycerides were similar between groups. Ospemifene also had beneficial effects on coagulation factors, including fibrinogen and protein C antigen, at all 3 time points ($p \leq 0.003$), although none of the changes represented values outside of normal ranges [72].

In the pooled safety analysis of 6 phase 2/3 trials, cardiovascular TEAE rates including DVT, cerebrovascular accident, and cerebral hemorrhage were low in both the ospemifene and placebo groups (0.3% vs 0.1%) [65]. This analysis, too, had a maximum follow-up of 52 weeks. It should be noted that longer periods of observation in larger populations are needed to provide definitive risk profiles regarding cardiovascular and thrombotic events, including VTEs and stroke.

4.4. Breast

Long-term breast safety was assessed in the phase 3 extension trials using mammography and breast examination/palpation to identify breast tenderness or breast mass after ospemifene treatment for up to 52 weeks or at study withdrawal [45–47]. One patient receiving ospemifene 60 mg (1.4%) had an abnormal mammography finding, which resolved by study end; another woman had an abnormal finding on breast palpation; all other exams were normal [46]. One case of breast cancer in situ was observed in the placebo group [46]. None of these studies reported any cases of breast cancer among women taking ospemifene [45–47]. Breast density data were not collected [46,47].

Breast pain was reported as an AE in 1.1% of women taking ospemifene ($n = 4$) compared with 0% taking placebo [45]. One woman receiving ospemifene had a breast mass that was ongoing at 56 weeks (4 weeks after the last study drug dose); follow-up mammography was found to be normal [45]. The event was deemed mild and unlikely to be related to the study drug [45]. Other breast-related TEAEs in ospemifene recipients, all considered mild, included breast mass ($n = 2$ [3.2%] in the 30-mg group; and $n = 1$ [1.4%] in the 60-mg group), breast microcalcification ($n = 1$ [1.4%], 60-mg group), and abnormal mammography finding ($n = 1$ [1.4%], 60-mg group), which resolved by the end of the study [46].

In the pooled safety analysis of 6 phase 2/3 trials, breast-related safety was comparable between the ospemifene and placebo groups including TEAE rates (2.5% vs 2.2%) and abnormal (but not clinically significant) findings at 12 months (7.8% vs 8.5%); there were no cases of breast cancer in the treatment group [65]. No significant increases in breast tenderness and no cases of breast cancer were reported in the meta-analysis of 6 RCTs [66].

Although no significant differences were seen for ospemifene versus placebo with respect to breast tenderness, abnormal mammograms, or breast cancer [45–47,66], the effect of ospemifene on the breast and the risk of breast cancer cannot be definitively assessed from the published ospemifene studies because of an inadequate sample population, short observation duration, and low incidence of breast cancer.

4.5. Bone

Double-blind phase 2 studies of bone biomarkers suggest decreased bone turnover with ospemifene. A study of 176 healthy postmenopausal women receiving various doses of ospemifene (30, 60, or 90 mg) or placebo for 3 months showed dose-dependent decreases in markers of bone resorption and bone formation [73]. Another phase 2 study in 118 women compared 3 doses of ospemifene versus 60 mg raloxifene and confirmed beneficial effects on bone with ospemifene similar to those with raloxifene [74].

In a pooled analysis of phase 2/3 trials of ospemifene versus placebo with treatment duration up to 52 weeks, there was a low incidence of vertebral or other fracture-related TEAEs that was comparable between groups (1.2% vs 1.5%, respectively), and there were no discontinuations because of bone-related TEAEs in either group [65]. Long-term data are needed on bone density and fracture prevention [74].

5. Conclusions

We conclude that the cumulative efficacy and safety data reviewed here support ospemifene for the treatment of menopausal vaginal dryness, the most prevalent symptom of VVA. Such data include significant improvements in multiple objective and subjective measures of VVA (eg, vaginal cell populations, vaginal pH, relief of dyspareunia or dryness, vulvar-vestibular imaging, and sexual function), and a good safety and tolerability profile, including breast, VTE, cardiovascular, and bone safety. The ability to treat vaginal dryness due to menopause should help improve vaginal health and quality of life, including sexual function, of women suffering from menopausal VVA.

6. Expert opinion

VVA is an important component of VVA/GSM in postmenopausal women, and unlike VMS, is unlikely to resolve over time without intervention [2,3]. Vaginal dryness is even more prominent than dyspareunia in VVA [7–9,17], with VVA having a significant impact on quality of life [2,3,6,8,9,12]. Evidence demonstrates that ospemifene improves vaginal moisture distinct from the effects of lubricants [38,41], as lubricants may provide temporary symptom relief but do not treat the underlying pathophysiology of VVA, and in some cases may cause irritation [2]. Structural improvements were documented in vaginal and vulvar tissues upon visual examination and imaging studies after ospemifene [39,47,52–55], and histologic studies demonstrated similar improvements in vulvar and vaginal tissue for epithelial layer thickness, proliferation index, and collagen content [56,57]. Elective use of lubricants during phase 3 trials decreased more over time in ospemifene than in placebo groups, presumably because they were less necessary [38,39,52]. Also of note, placebo patients had no improvements in VMI or vaginal pH regardless of lubricant use, suggesting that nonhormonal lubricants do not influence underlying VVA pathophysiology [52].

Significant improvements in the 4 co-primary endpoints of vaginal superficial cells, parabasal cells, pH, and MBS were found in all of the phase 3 trials [38–41,47]. Although multiple parameters support the benefit of ospemifene for indicators of VVA, it may be that vaginal pH alone can be used to diagnose VVA or as a single marker of physiologic and symptom improvement. A vaginal estradiol study recently published by Tucker et al found that change in vaginal pH up to week 12 significantly correlated with changes in parabasal cells, dyspareunia severity, and vaginal dryness severity, but negatively correlated with changes in superficial cells [75].

Ospemifene has a positive effect on sexual function, presumably due to physiologic improvements in vulvar and vaginal tissues. Treatment also significantly improved FSFI total and all subdomain scores in both an overall ITT population and women with dyspareunia as their MBS, and nonsignificantly improved these parameters in women with vaginal dryness as their MBS [58]. The observed benefits in FSFI likely reflect improvements in vaginal health and reduction in severity of VVA rather than changes in sex hormone levels [58], since ospemifene did not alter serum sex hormone levels [47,58].

Androgens as well as estrogens contribute to genitourinary health in women, given that testosterone and androstenedione are necessary precursors for estradiol and estrone, and deficiency of both hormones with aging and after menopause contributes to GSM [76]. Many vulvar and vaginal tissues have both estrogen and androgen receptors [53], and postmenopausal women have greater production of androgens than estrogens [76]. An expert panel of the International Society for the Study of Women's Sexual Health (ISSWSH) noted that because ARs are detected throughout the genitourinary system and different tissues exhibit varying AR and ER regulation, a more holistic understanding of the role of sex steroid hormones in GSM is needed [76]. In fact, data suggest that ospemifene may induce synthesis of androgen-dependent structural and functional proteins due to cross-regulation between ARs and ERs [53]. For example, ARs are more abundant (and ERs are less abundant) in epidermal cells of labia majora and minora than in vaginal epithelium [77], and imaging studies suggest that ospemifene can restore or regrow some vulvar structures, particularly the labia minora, and improve the appearance of androgen-sensitive tissue such as the vestibular glands seen on vulvar-vestibular imaging [55]. Preclinical studies showed that lasofoxifene, another SERM, significantly increased vaginal mucus formation without an increase in endometrial cell proliferation in the rat vagina or uterus, and that these changes were mediated by a significant increase in AR as well as ER- β protein levels [78]. Additionally, ospemifene counteracted the decrease in AR-expressing cells due to estradiol in breast tissue cultures [44]. If a positive effect on ARs can be confirmed for ospemifene in postmenopausal women, this mechanism may distinguish ospemifene from some approved treatments for VVA and GSM, such as vaginal estradiol, that are solely directed at the ER [55].

Data indicate the potential for ospemifene to improve the urinary component of GSM in addition to vaginal dryness and dyspareunia. Vulvoscopic and vulvar-vestibular images showed improvements in multiple anatomic areas including the urethral meatus after ospemifene treatment, an effect that may be due in

part to the effects of ospemifene on tissues with ARs [53,55]. Clinical data published in the past few years from a group of investigators in Italy provide evidence that ospemifene may affect urinary tissues in postmenopausal women. One study showed that 12 weeks of ospemifene versus no ospemifene significantly improved urgency symptoms in 81 women surgically treated for mixed urinary incontinence [79]. Another study showed that 6 months of ospemifene significantly reduced recurrent UTIs in 39 women with GSM; these women also had improvements in sexual function with ospemifene [80]. A retrospective analysis found that 12 weeks of ospemifene significantly reduced urgency and other overactive bladder symptoms in postmenopausal women with VVA ($n = 46$) [81]. Further study of ospemifene as a potential treatment for the urinary component of GSM is warranted.

Ospemifene carries a boxed warning regarding endometrial cancer and cardiovascular risk because of its estrogenic properties [31]. However, no reported cases of endometrial cancer have occurred in up to 1 year of follow-up [66,67]. Rare cases of endometrial simple hyperplasia without atypia have an incidence (0.3%) well below the rate of $\leq 1\%$ specified for postmenopausal women in the FDA guidance for VVA trials [47,67,68] and increases in endometrial thickness, even when statistically significant, are small (< 1 mm) and not clinically meaningful [66]. VTE risk in the ospemifene label may also be overstated. Although the SERM class, including ospemifene, has been shown to increase the risk of VTE by about 2-fold [31,70,71], no cases of VTE were reported in the 40- and 52-week extension studies of ospemifene versus placebo [45,46], and a pooled safety analysis showed low cardiovascular TEAE rates for ospemifene and placebo (both $\leq 0.3\%$) [65].

The ospemifene label in the US also warns against use in women with known or suspected breast cancer [31]. However, individual trials and pooled analyses of long-term breast safety reported no cases of breast cancer among women taking ospemifene, and similar rates of breast-related TEAEs between study groups; TEAEs that did occur were generally mild and resolved by study end [45–47,65]. Preclinical studies also indicated that ospemifene had a neutral effect or inhibited breast tumor growth [33,34,36,37,42–44]. Critics of the boxed warning observe that a deleterious effect on the breast is unlikely with ospemifene given that all SERMs tested to date have demonstrated reduced breast cancer incidence compared with placebo [69]. The US FDA label is concordant with the European label, which indicates that ospemifene is contraindicated for women with suspected breast cancer or current active treatment for breast cancer [32].

Perhaps the only undeniable outcome of the boxed warning for ospemifene (regarding endometrial, cardiovascular, and breast risk) is that many women will be unduly alarmed and either not seek treatment or not comply with the medication [24]. On the other hand, ospemifene treatment appears to be well accepted by women in addition to being effective and safe. In the recent Women's EMPOWER survey of 1858 women currently or previously being treated for VVA (with systemic HT, vaginal estrogen, OTC products, or lubricants/moisturizers), those who expressed the highest level of satisfaction were those taking ospemifene [7].

Taken together, the preclinical and clinical data reviewed here support the approval of ospemifene for the treatment of vaginal

dryness due to menopause, with regard to efficacy and overall safety, including breast, cardiovascular, and bone safety. Use of ospemifene would be advantageous for women who prefer an oral medication, as potential risks with its use are different from those with use of estrogen therapies. As a SERM and as data described above imply, use of ospemifene for the clinical signs of VVA does not potentially increase breast or endometrial cancer risk, and may also improve bone health. However, the daily use of ospemifene may increase the incidence of hot flashes in some women, and should be discussed with women are prescribed it, acknowledging the fact that oral estrogens alleviate hot flashes while treating VVA/GSM. We propose that the most suitable population of women for ospemifene would be those age 52–70 years with symptoms of VVA such as vaginal dryness, burning, and itching, and pain with intercourse, who may prefer an oral medication, and/or may also be concerned about an increased risk for breast cancer with estrogen-containing therapies. Additionally, a women's bone mass and risk for fracture, as well as breast cancer risk, may be issues to consider in women with symptomatic VVA/GSM, so that they can be counseled accordingly. Larger prospective studies of ospemifene are needed in these populations, given that other evidence-based options for high risk of breast cancer and diagnosed osteoporosis are approved and available.

We speculate that 5 years from now, we will have more numerous, longer-term data for a better understanding of the best way to counsel women on the use of newer drugs for VVA/GSM including ospemifene; that future use of proteomic and genomics (such as polymorphisms of the AR that may be associated with hormonally-mediated vestibulodynia) may lead to very novel treatment targets, although this may take more than 5 years; and that better patient-reported outcomes may be available to evaluate the full impact of VVA/GSM on a woman's quality of life so that we can move beyond the use of the MBS criterion. We believe our understanding of longer-term use of ospemifene and vaginal estrogens in 5 years will provide a clearer picture of risk/benefit – perhaps even informing product label changes. The decline in HT use for treatment of bothersome and distressing symptoms of GSM since the first publication of the WHI results has led to high levels of sexual pain, vaginal dryness, reduced libido, reduced orgasm intensity, and reduced pleasure during sexual activity, which is in contrast to the numerous oral, injectable, and mechanical devices available for treating male sexual dysfunction. In closing, we speculate that in the next 5 years, women and healthcare providers will recognize that comparing the risks and benefits of treating women in menopause with GSM, the life quality benefits will far outweigh the risks and more and more women will utilize treatments for GSM, such as ospemifene.

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Declaration of interest

DF Archer consults for AbbVie, Actavis, Agile Therapeutics, Bayer Healthcare, Endoceutics, Exeltis, InnovaGyn, Merck, Pfizer, Radius Health, Sermonix, Shionogi, Teva Women's Healthcare, and TherapeuticsMD; and has received research support from Actavis, Bayer Healthcare, Endoceutics, Glenmark, Merck, Radius Health, Shionogi, and TherapeuticsMD. JA Simon has served (within the past year, or current) as a consultant/advisor to AbbVie, Allergan plc, AMAG, Amgen, Ascend Therapeutics, Bayer Healthcare, CEEK Enterprises, Covance, Dare Bioscience, Duchesnay, Hologic, KaNDy/NeRRe Therapeutics, Mitsubishi Tanabe, ObsEva SA, Palatin Technologies, Sanofi SA, Shionogi, Sprout, and TherapeuticsMD; has received (within the past year, or current) grant/research support from AbbVie, Agile Therapeutics, Allergan plc, Bayer Healthcare, Endoceutics, GTX, Ipsen, Myovant Sciences, New England Research Institute, ObsEva SA, Palatin Technologies, Symbio Research, TherapeuticsMD, and Viveve Medical; has also served (within the past year, or current) on the speaker's bureaus of AbbVie, AMAG, Duchesnay, Novo Nordisk, Shionogi, and TherapeuticsMD; and is a stockholder (direct purchase) in Sermonix Pharmaceuticals. DJ Portman consults for Duchesnay, Agile Therapeutics, ITF Research Pharma, Sebel, Endoceutics, and AMAG; has received research support from Palatin, Endoceutics, Shionogi, TherapeuticsMD, and Population Council; is on the speaker's bureau for AMAG and TherapeuticsMD; and is currently Chief Executive Officer of Sermonix with stock/stock options. SR Goldstein is on the advisory board of AbbVie, AMAG, and TherapeuticsMD; consults for Cook ObGyn, Cooper Surgical, and IBSA; and has served on the speaker's bureau of AMAG, Duchesnay, and TherapeuticsMD. I Goldstein has received research support from AMAG, Endoceutics, Ipsen, and Strategic Science & Technologies; serves as consultant/advisor to Duchesnay, Ipsen, Shionogi, Strategic Science & Technologies; and is on the speaker's bureau for AMAG. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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