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## REVIEW ARTICLE

# Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence

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**Abstract**

***Objective:*** Treatment of menopausal symptoms by compounds with tissue-selective estrogen agonist/antagonist effects, often called selective estrogen receptor modulators, has been researched as an alternative to the use of estrogen therapy. These structurally diverse molecules elicit tissue-dependent responses in hormone-responsive tissues and organs, exhibiting variations in estrogenic activity in preclinical models of postmenopausal reproductive tissues that may improve postmenopausal women's health (eg, prevention and treatment of breast cancer, osteoporosis, and vulvar and vaginal atrophy).

***Methods:*** This literature review investigates whether preclinical data predicted the clinical effects of ospemifene on female reproductive and urinary tract tissues and compares these findings with the specific vaginal effects of other estrogen receptor agonists/antagonists (tamoxifen, raloxifene, and bazedoxifene) in preclinical and clinical studies. Lasofoxifene, although not currently available, is included because of its unique effects on vaginal tissue.

***Results:*** The response of endometrial and vaginal tissues to estrogen receptor agonists/antagonists can be differentiated using transvaginal ultrasound, endometrial histopathology, cytologic examination of vaginal smears, assessment of physical changes in the vagina, and relief of symptoms associated with vulvar and vaginal atrophy (such as dyspareunia).

***Conclusions:*** Available evidence indicates that ospemifene has unique effects on tissue, leading to a favorable long-term profile for the relief of vulvar and vaginal atrophy compared with other estrogen receptor agonists/antagonists (eg, tamoxifen, raloxifene, and bazedoxifene) with no short-term concerns about endometrial safety (based on endometrial hyperplasia, carcinoma, endometrial spotting, and endometrial bleeding).

***Key Words:*** Dyspareunia – Endometrium – Vulvar and vaginal atrophy – Urinary tract – Estrogen receptor agonist/antagonist – Selective estrogen receptor modulator.

Up to 50% of postmenopausal women experience vulvar and vaginal atrophy (VVA), a long-term condition caused by estrogen deficiency that is characterized by histologic vaginal changes such as epithelial thinning, decreased squamous cell maturation, and increased pH; VVA symptoms negatively impact women's quality of life.[1-3] VVA is thought to be a progressive condition that does not resolve without treatment.[4] In postmenopausal women, estrogen deficiency also adversely affects other tissues (eg, musculoskeletal, uterine, and urinary tract tissues,[1-4] increasing the risk for osteoporosis, fracture, recurrent urinary tract infection, and urinary incontinence).

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Low-dose vaginal estrogen-based prescription treatments and nonprescription vaginal lubricants and moisturizers are currently recommended as first-line treatment of VVA when only vaginal symptoms are present.[5,6] Vaginal estrogen interventions restore vaginal physiology and improve the vaginal microbiome, providing relief of bothersome symptoms such as vaginal dryness and dyspareunia.[7,8] Compounds with tissue-selective estrogen agonist/antagonist effects, often called selective estrogen receptor modulators, have been developed to elicit benefits in target tissues while minimizing offtarget adverse effects. Ospemifene is an estrogen receptor agonist/antagonist (ERAA) that was recently approved by the US Food and Drug Administration for the treatment of moderate to severe dyspareunia, a symptom of VVA caused by menopause. Ospemifene has been recommended as an option for therapy in the 2013 North American Menopause Society guidelines for the treatment of symptomatic VVA.[6]

The objectives of this review are to describe the effects of ospemifene on female reproductive and urinary tract tissues and to assess the utility of preclinical models in predicting ERAA effects on end organs in humans. The preclinical and clinical findings for ospemifene and several other ERAAs, including tamoxifen, raloxifene, bazedoxifene (in combination with conjugated estrogens [CE]), and lasofoxifene, will be described.

## SEARCH METHODOLOGY

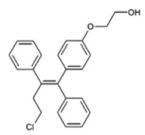
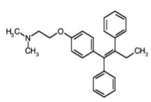
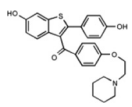
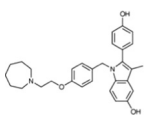
Relevant articles in English were identified via a search of PubMed from 1990 to 2013 using the search string "(Selective Estrogen Receptor Modulator OR SERM) AND (Vagina OR Vulvar OR Endometrium OR Uterus OR Uterine OR Bone OR Breast OR Brain OR Urinary OR Urogenital)," including clinical trials, guidelines, meta-analyses, and systematic reviews but excluding case reports and letters. Additional references of interest were identified by manual review of cited reference lists and PubMed searches of individual ERAAs.

## ERAA MECHANISM OF ACTION

Biological effects of ERAA's are mediated through binding and activation of intracellular estrogen receptors (specifically estrogen receptor-α [ER-α], estrogen receptor-β [ER-β], or both) that function as nuclear ligand–inducible transcription factors.[9] After ligand binding, a conformational change in estrogen receptor leads to recruitment of coregulator proteins, transcription factors, and chromatin remodeling factors responsible for regulation of gene expression.[10] Importantly, ERAAs may exert a mix of agonist, antagonist, or neutral biological effects (Tables 1 and 2) because the response pathway in a given tissue depends on estrogen receptor subtype (eg, ER-α–selective vs ER-β–selective ERAAs), the structure and shape of the ligand-receptor complex, and the functional cooperation of the gene promoter with cell type–specific transcriptional coactivators (mimicking estrogenic activity) and corepressors (suppressing estrogenic activity; Fig.).[69-74] As agonist/antagonist effects of ERAAs depend on dose, relative doses in animals and humans also should be considered when assessing the prediction of clinical effects from preclinical data.

Although ERAAs exhibit potentially beneficial effects on a number of tissues that are important for postmenopausal women's health,[75] we will principally consider the effects of each ERAA on the vaginal epithelium; on uterine, endometrial,

**TABLE 1.** *Effects of selected ERAAs on target tissues in animals*

| | | Effects on target tissue | | | | |
|---|---|---|---|---|---|---|
| ERAA | Chemical structure | Uterine weight | Endometrium | Vagina | Breast | Bone |
| Ospemifene |  | Neutral[11,12]<br>Partial agonist[13,14] | Neutral[12]<br>Partial agonist[11] | Agonist[13] | Antagonist[14-17] | Neutral (OCF)[18]<br>Antagonist (BR)[14]<br>Agonist (BF)[19] |
| Tamoxifen |  | Agonist[11,20-23] | Neutral[20]<br>Agonist[26-29] | Agonist[24] | Antagonist[25] | Agonist (BF)[18,21]<br>Antagonist (OCF)[18] |
| Raloxifene |  | Neutral[11,20,23,27,30,31]<br>Partial agonist[13,36] | Neutral[20,27,32]<br>Partial agonist[11,31,36] | Neutral[33] | Antagonist[34,35] | Neutral (OCF)[18]<br>Agonist (BF)[32,37]<br>Antagonist (BR)[30,32] |
| Bazedoxifene |  | Partial agonist[38]<br>Antagonist[42] | Neutral[39]<br>Antagonist[42] | ND | Antagonist[40,41] | Agonist[38] |

ERAA, estrogen receptor agonist/antagonist; OCF, osteoclast formation; BR, bone resorption; BF, bone formation; ND, no data.

**TABLE 2.** *Effects of selected ERAAs on target tissues in humans*

| ERAA | Effects on target tissue | | | |
|---|---|---|---|---|
| | Endometrium | Vagina | Breast | Bone |
| Ospemifene | Partial agonist[43-46]<br>• Up to 52-wk RCT<br>• Slight ↑ in thickness from BL by TVU<br>• Generally no histologic changes from BL<br>• No reports of cancer | Agonist[43-46]<br>• Up to 52-wk RCT<br>• SS ↑ in superficial cells<br>• SS ↓ in parabasal cells<br>• SS ↓ in pH<br>• $P < 0.001$ for all vs PBO | Neutral (limited data)[43-46]<br>• Up to 52-wk RCT<br>• No clinically significant abnormalities by mammography<br>• No reports of cancer during these RCTs[a] | Agonist (limited data)[47,48]<br>• 3-mo RCT<br>• Positive effects of bone turnover on biomarkers |
| Tamoxifen | Agonist[49-51]<br>• Meta-analysis of four trials<br>• SS ↑ in cancer ($P < 0.001$) vs PBO<br>• ↑ in thickness[b] | Agonist[52]<br>• Prospective study<br>• SS ↑ in MI across 24 mo vs controls ($P < 0.0001$) | Antagonist[51]<br>• Meta-analysis of four trials<br>• SS ↓ in cancer vs PBO ($P < 0.0001$) | Agonist[53]<br>• 2-y RCT<br>• SS ↑ in lumbar spine BMD vs PBO ($P < 0.001$)<br>• SS ↓ in serum osteocalcin from BL vs PBO ($P < 0.001$) |
| Raloxifene | Neutral or antagonist[51,54-58]<br>• Meta-analysis of three trials<br>• No difference in thickness by TVU and in incidence of bleeding vs controls<br>• No increase in cancer | Neutral[54,59]<br>• Up to 6-mo CT<br>• No difference in VMV or parabasal, intermediate, or superficial cells by smear vs controls | Antagonist[51]<br>• Meta-analysis of five trials<br>• SS ↓ in all breast cancers ($P < 0.0001$) | Agonist[60,61]<br>• Up to 24-mo RCT<br>• SS ↑ in BMD vs PBO or BL ($P < 0.05$)<br>• SS ↓ in biomarkers of bone turnover vs PBO or BL ($P < 0.05$) |
| Bazedoxifene (monotherapy) | Antagonist[62]<br>• 7-y RCT<br>• No difference in thickness by TVU and in incidence of hyperplasia vs PBO<br>• SS ↓ in incidence of cancer vs PBO ($P = 0.02$) | Antagonist[63]<br>• 12-wk RCT<br>• Little change in superficial cells vs BL; parabasal cells increased; intermediate cells decreased[c] | Neutral or antagonist [64,65]<br>• 24-mo RCT<br>• No ↑ in density by mammography vs PBO<br>• No difference in cancer rates or pain vs PBO | Agonist[66-68]<br>• Up to 5-y RCT<br>• SS ↓ in incidence of new vertebral fractures vs PBO ($P < 0.05$)<br>• SS ↑ in lumbar spine BMD vs PBO ($P \leq 0.023$)<br>• SS ↓ in serum osteocalcin/CTX vs PBO ($P \leq 0.009$) |

ERAA, estrogen receptor agonist/antagonist; RCT, randomized clinical trial; (↑) increase; BL, baseline; (↓) decrease; TVU, transvaginal ultrasound; SS, statistically significant; PBO, placebo; MI, maturation index; BMD, bone mineral density; CT, clinical trial (randomized or not); VMV, vaginal maturation value; CTX, type 1 collagen C-telopeptide.

[a]Total N equals 1,384.

[b]One 2-year RCT and one 5-year longitudinal study (median treatment time, 24 mo).[49,50]

[c]No statistical testing was performed versus PBO.[63]

and ovarian tissues; and on the female urinary tract to differentiate those agents that are most likely to be beneficial without posing short-term or long-term safety concerns.

## VAGINAL EFFECTS

### Preclinical data

Ospemifene (10 mg/kg/d for 2 wk) had a more pronounced effect than raloxifene (10 mg/kg/d) on increasing the thickness and mucification of the vaginal epithelium in a commonly used ovariectomized rat model.[13] Similar morphologic changes were observed with continuous subcutaneous tamoxifen infusion (150 μg/d for 2 wk).[24] Systemic CE 0.1 mg/kg/day resulted in higher vaginal epithelium maturation scores, but raloxifene (1 mg/kg/d for 35 d) did not,[33] suggesting that raloxifene has no clear estrogenic effect on the vaginal epithelium, unlike ospemifene and tamoxifen.

### Clinical data

The effects of ospemifene on reproductive tissues in postmenopausal women have been investigated in three phase 3 multicenter, randomized, double-blind, clinical trials. In one 12-week study, 826 women with a low vaginal maturation index (MI; ie, ≤5% superficial cells on vaginal smear) and a vaginal pH higher than 5.0 were randomized to receive ospemifene or placebo.[43] In a second 12-week study, ospemifene 30 and 60 mg/day elicited a statistically significant improvement in vaginal MI, as assessed by increases in superficial cells (7.8% and 10.8%, respectively) and decreases in parabasal cells (21.9% and 30.1%, respectively), compared with the effects of placebo (increase in superficial cells [2.2%] and parabasal cells [3.98%]; $P < 0.001$ for all). Vaginal pH decreased whereas vaginal dryness and dyspareunia improved, with each symptom measured on a scale from 0 to 3 (0, none; 1, mild; 2, moderate; 3, severe). Clinical benefits on vaginal MI and pH were independently confirmed in another 12-week trial of ospemifene 60 mg/day in postmenopausal women (N = 919) with self-reported moderate to severe dyspareunia (n = 605)[44] or vaginal dryness (n = 314).[45] Women treated with ospemifene also reported a more pronounced relief of dyspareunia (on the same scale from 0 to 3) on week 12 compared with placebo

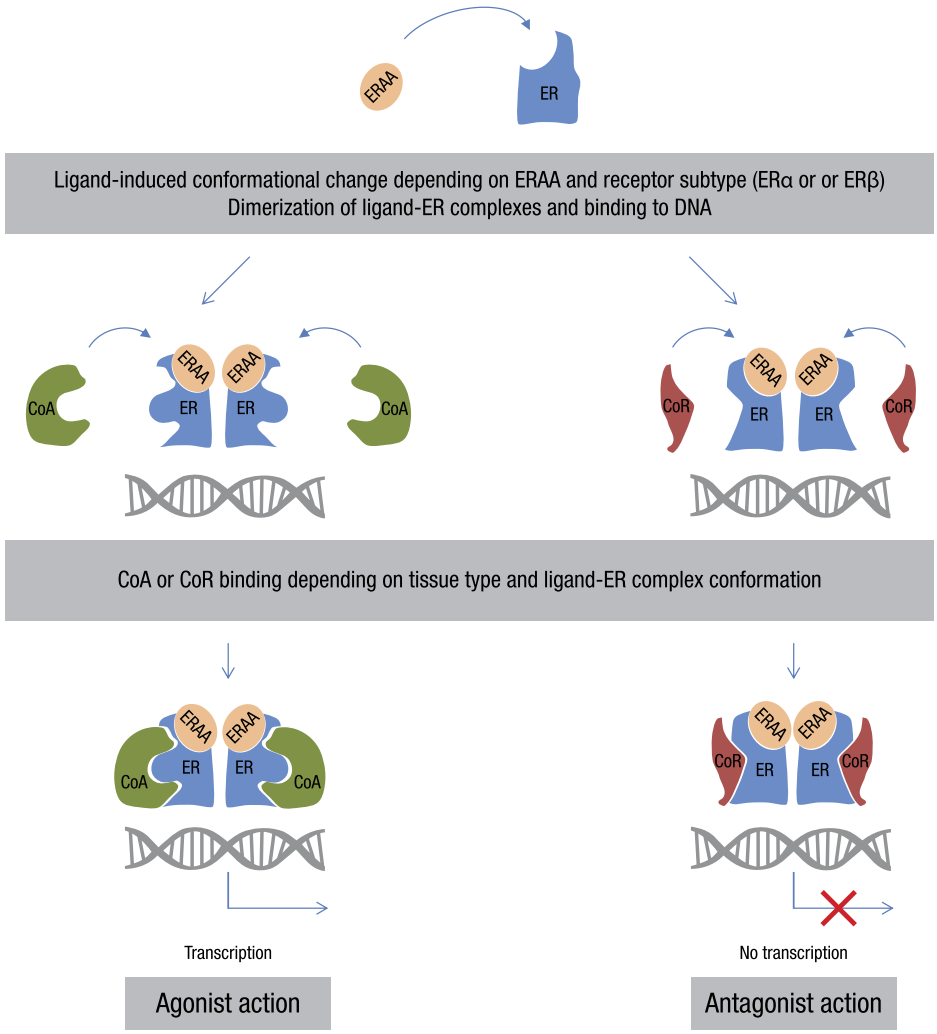



**FIG.** Estrogen receptor agonist/antagonist mechanism of action via binding to the ER-α or ER-β receptor and eliciting specific nuclear coactivators and corepressors. ERAA, estrogen receptor agonist/antagonist; ER, estrogen receptor; CoA, coenzyme A.

(−1.5 vs −1.2; $P = 0.0001$),[44] and use of a nonhormonal lubricant (as needed) was less frequent.[43] A 12-month, randomized, double-blind study demonstrated that ospemifene 60 mg/day significantly improved vaginal MI at 12, 26, and 52 weeks and was associated with a more pronounced decrease in vaginal pH at each time point compared with placebo (N = 426; $P < 0.0001$ for all comparisons).[46] After 12 months, women treated with ospemifene exhibited significant improvement in physical changes associated with VVA (ie, petechiae, pallor, friability, vaginal mucosal dryness, and redness) compared with placebo ($P < 0.0001$).[46] Sexual function was assessed in the second study using the validated Female Sexual Function Index; on week 12, ospemifene significantly improved all Female Sexual Function Index domains (desire, arousal, lubrication, orgasm, satisfaction, and pain reduction; $P < 0.05$ vs placebo).[76]

In contrast to ospemifene, bazedoxifene monotherapy has not demonstrated efficacy for the treatment of VVA. The phase 3 Selective estrogens, Menopause, And Response to Therapy (SMART)-3 study found that bazedoxifene 20 mg/day alone had no effect on vaginal pH on week 12.[63] Bazedoxifene monotherapy did not improve responder rates (vaginal superficial cells >5%, vaginal pH <5, and/or improvement in the most bothersome symptom by ≥1 category from baseline) on week 12 (58%) compared with placebo (66%). Similarly, bazedoxifene did not improve measures of sexual function (eg, ease of lubrication, physical function, and satisfaction with orgasm) in further analyses from the same study compared with placebo.[77]

Bazedoxifene, in combination with CE, is approved for the treatment of moderate to severe vasomotor symptoms associated with menopause and for the prevention of postmenopausal osteoporosis.[78] Owing to its antagonistic effects on estrogen receptors in the genitourinary tract, bazedoxifene is combined with CE for endometrial protection; however, bazedoxifene reduces the beneficial effects of CE on VVA. Improvements in VVA and menopausal symptoms were observed with bazedoxifene 10 and 20 mg/day in combination with CE 0.625 and 0.45 mg/day, compared with placebo, in postmenopausal women enrolled in the phase 3 SMART-1 trial.[79] In the phase 3 SMART-3 trial, bazedoxifene 20 mg/day

with CE 0.625 or 0.45 mg/day significantly increased superficial cells, decreased parabasal cells, and improved vaginal dryness, compared with placebo, on week 12 ($P < 0.01$, $P < 0.001$, and $P < 0.05$, respectively).[63] Bazedoxifene 20 mg/day with CE 0.625 mg/day, but not the dose approved for the treatment of vasomotor symptoms and osteoporosis (bazedoxifene 20 mg/d with CE 0.45 mg/d), significantly improved vaginal pH ($P < 0.001$) and participant-reported most bothersome VVA symptom ($P = 0.048$) compared with placebo.[63,78] Bazedoxifene with CE is not approved for the treatment of VVA despite the benefits found, particularly at the higher dose. In a related study, bazedoxifene 20 mg/day with CE 0.625 or 0.45 mg/day was associated with a significant improvement in ease of lubrication (assessed with the Arizona Sexual Experiences scale) from baseline to week 12 compared with placebo ($P < 0.05$); however, there was no difference in any change in the total Arizona Sexual Experiences scale score versus placebo.[77] Results from the Menopause-Specific Quality of Life questionnaire on week 12 showed significant improvements in vasomotor function, sexual function, and total scores with either dose of bazedoxifene with CE versus placebo ($P < 0.01$) or bazedoxifene 20 mg alone ($P < 0.001$).

Treatment with raloxifene monotherapy does not improve VVA, in contrast with ospemifene and bazedoxifene/CE. Raloxifene (60 mg/d) in postmenopausal women treated for 3 to 6 months had no effect on vaginal MI.[54,59] Raloxifene monotherapy for 6 months in postmenopausal women with osteoporosis did not affect the vaginal epithelium.[59] Raloxifene alone also did not increase vaginal bleeding (endometrial), spotting, or discharge even after administration for 3 years[55]; thus, it seems to have a safe vaginal profile. Although raloxifene, in combination with a local estrogen, is not approved for the treatment of VVA, the addition of raloxifene with vaginal CE cream in a 3-month study and of an estradiol ring in a 6-month trial did not counteract the local symptomatic or objective estrogenic effects of vaginal estrogens.[80,81]

Postmenopausal women with breast cancer who received tamoxifen for 2 years showed significant improvement in vaginal MI compared with control groups but also had an increased prevalence of endocervical hyperplasia.[52] In the ATAC ('Arimidex,' Tamoxifen, Alone or in Combination) trial, postmenopausal women treated with tamoxifen for 5 years reported vaginal dryness (9.1%) and dyspareunia (8.1%), although these rates were lower than those reported with the comparator anastrozole (18.5% and 17.3%, respectively).[82] In summary, the positive effects of ospemifene on vaginal tissue differ from those of other ERAAs, such as the mixed effects of tamoxifen, the neutral effects of raloxifene, and the mild negative effects of bazedoxifene alone.

**TABLE 3.** *Binding potencies of estradiol and selected ERAAs for ER-α and ER-β receptors*

| | | $IC_{50}$ (nM) | |
|---|---|---|---|
| Study | Compound | ER-α | ER-β |
| Unkila et al[13] | Ospemifene | 827 | 1,633 |
| | Estradiol | 6.8 | 9.1 |
| Komm et al[38] | Bazedoxifene | 26 | 99 |
| | Estradiol | 3.2 | 3.6 |
| | Raloxifene | 2.4 | 43 |

ERAA, estrogen receptor agonist/antagonist; ER-α, estrogen receptor-α; ER-β, estrogen receptor-β; $IC_{50}$, concentration producing 50% inhibition.

## UTERINE, ENDOMETRIAL, AND OVARIAN EFFECTS

### Preclinical data

Studies in rodents suggest that the effects of ERAAs on uterine weight are dose-dependent and time-dependent. In mice, a single dose of tamoxifen 3 mg/kg significantly increased uterine weight similar to estradiol (138% and 141% of ovariectomized control, respectively) at 16 hours after administration, but ospemifene and raloxifene (3 mg/kg each) had no effects on uterine weight at the same time point.[11] Ospemifene (0.1-10 mg/kg/d for 28 d) caused dose-dependent increases (significant increases at 0.3-10 mg/kg) in uterine weight compared with raloxifene (3 mg/kg for 14 d) in ovariectomized rats.[14] Even so, the agonist effect of ospemifene (0.1-10 mg/kg) on uterine weight was only 37% of the increase noted with estradiol, consistent with the lower binding affinity of ospemifene, compared with estradiol, for ER-α (Table 3).[13] The dose-dependent increases in vaginal and uterine epithelial thickness with ospemifene were accompanied by morphohistologic changes in the vaginal epithelium (eg, mucification and vacuolization).[75] Bazedoxifene also exhibited a lower in vitro binding affinity, compared with estradiol, for both ER-α and ER-β; raloxifene inhibited ER-α to a similar degree as estradiol but was a weaker inhibitor of ER-β (Table 3).[38] When administered alone for 8 weeks, bazedoxifene decreased uterine weight in mice and exhibited no uterotrophic effects on a postmenopausal primate model.[39,42]

In ovariectomized rats, tamoxifen caused a dose-dependent (1-1,000 μg/kg) increase in uterine weight (concentration producing 50% activity [$EC_{50}$], 33.7 μg/kg) at 72 hours, which was accompanied by increased luminal epithelial thickness (at doses 30-1,000 μg/kg), stromal cell hypertrophy (10-1,000 μg/kg), epithelial hypertrophy and hyperplasia (30-1,000 μg/kg), increased glandular secretory activity (30-1,000 μg/kg), and mild edema (100-1,000 μg/kg).[26] A single dose (3 mg/kg) of tamoxifen, raloxifene, or ospemifene resulted in increased proliferation of luminal and glandular endometrial epithelial cells in ovariectomized rats.[11] In addition, in a postmenopausal primate model, administration of tamoxifen for 4 months caused a pronounced increase in endometrial thickness (similar to estradiol) that was accompanied by stromal fibrosis.[83]

Unlike the estrogenic response elicited by tamoxifen in the uterus, several preclinical studies showed that raloxifene did not significantly increase myometrial or stromal thickness or cause endometrial hyperplasia[20,27,32] even when administered for up to 2 years.[28]

Administration of bazedoxifene for 8 weeks caused a significant decrease in epithelial thickness and endometrial gland formation in the mouse uterus, consistent with previously described antagonistic effects on uterine weight.[42] Moreover, in

**TABLE 4.** *Endometrial thickness in women treated with ospemifene 60 mg/day versus placebo in phase 2 and phase 3 randomized, double-blind, placebo-controlled studies*

| Characteristic | Placebo (n = 543) | n | Ospemifene 60 mg/d (n = 851) | n |
|---|---|---|---|---|
| Endometrial thickness, mean (SD), mm | | | | |
| Baseline | 2.2 (0.8) | 538 | 2.1 (0.8) | 847 |
| 12 wk | 2.2 (1.2) | 367 | 2.6 (1.5) | 641 |
| 6 mo | 2.1 (1.1) | 92 | 2.6 (1.5) | 371 |
| 12 mo | 2.1 (1.0) | 85 | 2.8 (1.4) | 345 |
| Change from baseline in endometrial thickness, mean (SD), mm | | | | |
| 12 wk | 0.1 (1.2) | 365 | 0.5 (1.5) | 640 |
| 6 mo | <0.1 (1.3) | 92 | 0.6 (1.6) | 370 |
| 12 mo | 0.1 (1.2) | 85 | 0.8 (1.5) | 344 |
| Postbaseline endometrial thickness, n (%) | | | | |
| Any time postbaseline | | 458 | | 771 |
| ≥4 mm | 29 (6.3) | | 140 (18.2) | |
| ≥5 mm | 14 (3.1) | | 69 (9.0) | |
| ≥8 mm | 2 (0.4) | | 12 (1.6) | |
| Last observation[a] | | 458 | | 771 |
| ≥4 mm | 20 (4.4) | | 98 (12.7) | |
| ≥5 mm | 12 (2.6) | | 51 (6.6) | |
| ≥8 mm | 1 (0.2) | | 9 (1.2) | |

Data presented here are from the Integrated Summary of Safety conducted by Shionogi Inc. All authors had access to this report, and part of the data was presented at the International Menopause Society 14th World Congress on Menopause [Constantine G, Goldstein S, Graham S. Endometrial safety of ospemifene: results of the phase 2/3 clinical development program. In: International Menopause Society 14th World Congress on Menopause; May 1-4, 2014; Cancun, Mexico].
[a]Within 14 days of the last dose of the study drug.

the same study, bazedoxifene suppressed endometrial proliferation and caused regression of experimentally induced endometriosis. Interestingly, bazedoxifene (20 mg/d) with systemic conjugated equine estrogens (0.45 mg/d) for 20 months inhibited the development of endometrial hyperplasia and ER-α target genes in a postmenopausal primate model in which bazedoxifene alone showed no uterotrophic effects.[39]

Preclinical studies in rodents showed that tamoxifen (0.03 and 0.2 mg/kg/d for 2-4 wk) and raloxifene (75 and 365 mg/kg/d for 6 mo), but not bazedoxifene (3 mg/kg/d for 8 wk), induced the formation of ovarian cysts.[42,84,85] Ospemifene (3, 30, and 300 mg/kg/d for 26 wk) increased the number of ovarian cysts in rats. Two studies of ospemifene (100, 500, and 1,250 mg/kg/d for 4 wk; 15, 50, and 150 mg/kg/d for 39 wk) in primates demonstrated an elevated incidence of ovarian cysts in all dose groups. As discussed subsequently, however, preclinical findings of ovarian cysts did not always translate into clinical findings.

### Clinical data: effects on the endometrium

The long-term risk of developing endometrial hyperplasia is another concern with the use of ERAAs. Postmenopausal women (N = 826) randomized to receive ospemifene (30 and 60 mg/d) or placebo for 12 weeks exhibited modest changes from baseline in endometrial thickness (0.42 and 0.72 mm, respectively) compared with placebo (−0.02 mm).[43] These outcomes were independently confirmed in a second 12-week randomized study that compared ospemifene 60 mg/day with placebo.[45] The effects of ospemifene 60 mg/day on endometrial thickness are summarized in Table 4. Phase 3 clinical trials found no evidence of endometrial hyperplasia or carcinoma

**TABLE 5.** *AEs related to uterine polyp and vaginal bleeding in phase 2 and phase 3 randomized, double-blind, placebo-controlled studies of ospemifene 60 mg/day*

| Preferred term | Placebo | n | Ospemifene 60 mg/d | n |
|---|---|---|---|---|
| Women with intact uterus | | 543 | | 851 |
| Any uterine polyp TEAE, n (%) | 1 (0.2) | | 5 (0.6) | |
| Uterine polyp | 1 (0.2)[a] | | 5 (0.6)[a] | |
| Any vaginal bleeding and/or spotting TEAE, n (%)[b] | 5 (0.9) | | 10 (1.2) | |
| Vaginal hemorrhage | 5 (0.9) | | 7 (0.8) | |
| Coital bleeding | 0 | | 1 (0.1) | |
| Irregular menstruation | 0 | | 1 (0.1) | |
| Metrorrhagia | 0 | | 1 (0.1) | |
| Women without intact uterus | | 380 | | 391 |
| Any vaginal bleeding and/or spotting TEAE, n (%)[b] | 0 | | 1 (0.3) | |
| Vaginal hemorrhage | 0 | | 1 (0.3) | |

Data presented here are from the Integrated Summary of Safety conducted by Shionogi Inc. All authors had access to this report, and part of the data was presented at the International Menopause Society 14th World Congress on Menopause [Goldstein S, Archer D, Graham S. Safety of oral ospemifene in phase 2/3 placebo-controlled clinical trials. In: International Menopause Society 14th World Congress on Menopause; May 1-4, 2014; Cancun, Mexico].
AE, adverse event; TEAE, treatment-emergent adverse event.
[a]All uterine polyps were reported in a single study (incidence with placebo, 1/62 [1.6%]; incidence with ospemifene, 5/364 [1.4%])[46]; none were reported in the other studies included in phase 2/phase 3 analysis. Only one polyp (in the ospemifene group) was confirmed on further expert review, whereas the rest were considered artifacts.[46]
[b]Women with more than 1 TEAE that coded for the same preferred term were counted once for that preferred term.

in endometrial biopsies of postmenopausal women treated with ospemifene for 12 weeks.[43,44] Moreover, treatment with ospemifene for 52 weeks resulted in a low incidence (0.3%) of endometrial hyperplasia but no cases of carcinoma in women (n = 267) who had biopsies on week 52.[46] The endometrial safety profile of ospemifene 60 mg/day is summarized in Table 5.

Raloxifene, which is approved for the treatment and prevention of osteoporosis in postmenopausal women and for reduction of the risk of invasive breast cancer,[56] had no effect on endometrial thickness or proliferation compared with baseline when administered at a dose of 60 mg/day for 3 months.[54] Moreover, vaginal bleeding and spotting were not elevated in women who were treated with raloxifene 60 mg/day for up to 5 years (2.9%-3.3%) compared with untreated women (1.9%-3.6%).[55,57,58] Consistent with the lack of uterotrophic effects of raloxifene observed in preclinical studies (reviewed previously), there was no evidence of increased endometrial hyperplasia or carcinoma in postmenopausal women administered raloxifene for up to 8 years, although uterine polyps were significantly more common than with placebo.[86]

Bazedoxifene has a favorable long-term endometrial safety profile. In a phase 3 study, bazedoxifene (20 or 40 mg/d) for 7 years had minimal effects on endometrial thickness (−0.11 mm for bazedoxifene vs 0.07 mm for placebo) and endometrial hyperplasia (0.1% for all groups).[62] Similar to ospemifene, bazedoxifene (20 and 40 mg/d) for 7 years produced a lower rate of endometrial carcinoma compared with placebo (0.1% vs 0.4%; $P = 0.020$) and had negligible effects on endometrial hyperplasia (0.1% for both groups).[87]

The favorable endometrial safety profiles of ospemifene, bazedoxifene, and raloxifene are distinct from that of tamoxifen. Results from the ATAC breast cancer prevention trial showed that tamoxifen treatment caused a pronounced increase (from 3.8 mm at baseline to 7.0 mm after 2 y) in endometrial thickness.[49] Importantly, such effects persisted for approximately 3 years after the end of treatment.[50] Tamoxifen therapy (20-30 mg/d for approximately 3 y) was associated with higher incidences of endometrial hyperplasia (35.7% vs 5.6%; $P < 0.0001$) and endometrial cancer (21.5% vs 0.9%; $P < 0.0001$) in postmenopausal women with breast cancer who had gynecologic symptoms (vaginal bleeding or spotting), compared with similar participants without such symptoms.[88] A meta-analysis of nine breast cancer prevention trials found a higher incidence of endometrial cancer (hazard ratio, 2.18; 95% CI, 1.39-3.42; $P = 0.001$) during the first 5 years of follow-up with tamoxifen (ie, Marsden, International Breast Cancer Intervention Study-1, National Surgical Adjuvant Breast and Bowel Project, Prevention-1, and Italian trials) but no increased risk of endometrial cancer with raloxifene (ie, Multiple Outcomes of Raloxifene Evaluation/Continuing Outcomes Relevant to Evista, Raloxifene Use for The Heart, Study of Tamoxifen and Raloxifene, and Postmenopausal Evaluation and Risk Reduction With Lasofoxifene trials).[51] In fact, the Study of Tamoxifen and Raloxifene P2 study (an update to the Study of Tamoxifen and Raloxifene) found that the relative risks (RRs) for endometrial hyperplasia (RR, 0.19; 95% CI, 0.12-0.29) and endometrial cancer (RR, 0.55; 95% CI, 0.36-0.83; $P = 0.003$) with raloxifene (60 mg/d) were lower than those with tamoxifen (20 mg/d) across 5 years.[89] The endometrial safety profile of the ERAAs contrasts with that of CE 0.625 mg/day alone (endometrial hyperplasia rate of 21% after 1 y).[90] The risk of endometrial cancer is greatly elevated with longer use of unopposed or high-dose CE (overall risk ratio, 7.6; risk ratio with ≥7 y of use, 13.9).[91]

### Clinical data: effects on the ovaries

Consistent with preclinical observations, ovarian cysts were detected in 6.3% to 14.3% of postmenopausal women administered tamoxifen therapy for breast cancer.[92,93] However, no evidence of increased ovarian cyst formation was detected in postmenopausal women receiving bazedoxifene (20 or 40 mg/d) or raloxifene (60 mg/d) for 3 years.[94] In pivotal ospemifene studies, only one participant (0.1%; n = 1,242) developed ovarian cysts, which is well within the annual rate (2.6%) of spontaneous ovarian cyst formation found among postmenopausal women in a large, prospective, multicenter, cohort study.[95] In summary, rates of ovarian cyst formation with ospemifene, bazedoxifene, and raloxifene are within the background incidence rates for postmenopausal women, but may be increased with tamoxifen.

## URINARY TRACT EFFECTS

### Preclinical data

Varied effects of ERAAs on the urinary tract have been reported in preclinical studies. The urinary tract effects of ospemifene and raloxifene were assessed in ovariectomized rats using estradiol and placebo controls (data on file at Shionogi Inc). There were no statistically significant between-treatment differences in bladder pressure, flow rate, micturition time, amount of residual urine, or bladder capacity, suggesting that ospemifene and raloxifene had no effect on urodynamics. In a rat model of urinary incontinence caused by trauma during parturition, treatment with raloxifene (1 mg/kg/d) or 17β-estradiol (0.1 mg/kg/d) resulted in greater detrusor overactivity and urethral relaxation incontinence, compared with controls, suggesting that raloxifene and estrogen may worsen voiding patterns.[96] Others found no significant effect of raloxifene (1 mg/kg/d) or 17β-estradiol (0.01 mg/kg/d) on voiding patterns in the same rat model, suggesting a lack of specificity for this model.[97] In ovariectomized rats, raloxifene (750 μg/d for 30 d) significantly increased distal urethral epithelial thickness compared with vehicle control, suggesting a potential beneficial effect of raloxifene for postmenopausal urinary incontinence.[98] Additional studies are necessary to fully elucidate the effects of raloxifene on the urinary tract. Tamoxifen improved impaired bladder capacity and compliance in an animal model of chronic inflammatory bladder disease, in which ER-β was significantly decreased in a diseased bladder compared with a control bladder.[99]

### Clinical data

Although ERAAs have been reported to adversely affect the pelvic floor and to cause incontinence, urodynamics data are

**TABLE 6.** *TEAEs of the reproductive and urinary tracts in women (≥1%) treated with ospemifene 60 mg/day versus placebo in phase 2 and phase 3 randomized, double-blind, placebo-controlled studies*

| Preferred term | Placebo (n = 924) | Ospemifene 60 mg/d (n = 1,242) |
|---|---|---|
| Any TEAE, n (%)[a] | 496 (53.7) | 840 (67.6) |
| Urinary tract infection | 44 (4.8) | 81 (6.5) |
| Vaginal discharge | 4 (0.4) | 55 (4.4) |
| Vulvovaginal candidiasis | 5 (0.5) | 53 (4.3) |
| Vulvovaginal mycotic infection | 5 (0.5) | 38 (3.1) |
| Cystitis | 6 (0.6) | 23 (1.9) |
| Genital discharge | 1 (0.1) | 18 (1.4) |
| Vulvovaginal pruritus | 7 (0.8) | 18 (1.4) |
| Urinary tract infection bacterial | 6 (0.6) | 17 (1.4) |
| Vaginal infection | 6 (0.6) | 13 (1.0) |
| Vulvovaginal dryness | 1 (0.1) | 13 (1.0) |

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TEAE, treatment-emergent adverse event.
[a]Women with more than one TEAE that coded for the same preferred term were counted once for that preferred term.

limited, and no published study has identified clear effects.[100] The percentage of participants with improved urinary symptoms (eg, frequent urination, urine leakage, and difficulty in voiding) was similar among the ospemifene 30 mg, ospemifene 60 mg, and placebo groups in two 12-week studies. An integrated assessment of safety in phase 2 and phase 3 clinical trials showed that ospemifene 60 mg/day elicited low incidences of vaginal and urinary adverse outcomes (eg, discharge, infection, pruritus, dryness, urinary tract infection, and cystitis; Table 6). The rates of urinary tract infection, vaginal discharge, vulvovaginal candidiasis, and vulvovaginal mycotic infection seemed greater with ospemifene treatment than with placebo, although the absolute incidences were low. The low incidences of urinary tract infections and cystitis observed with ospemifene are consistent with the reduction in vaginal pH, indicating increased vaginal *Lactobacillus* colonization with reduction in the incidence of *Escherichia coli* in the vagina. More studies are necessary to delineate the effects of ospemifene on the urinary tract.

### Discontinued ERAAs

ERAAs that entered clinical development but failed to advance include compounds that failed to meet planned endpoints (eg, arzoxifene) and compounds that produced unacceptable adverse effects such as urinary incontinence and pelvic organ prolapse (eg, levormeloxifene and lasofoxifene).[101-104] Lasofoxifene demonstrated clinical efficacy for postmenopausal osteoporosis in phase 3 trials but was associated with gynecologic safety concerns (vaginal bleeding, increased endometrial thickness, and increased endometrial polyps).[105,106]

## DISCUSSION

ERAAs are structurally heterogeneous compounds that interact with estrogen receptors, which function as nuclear ligand–inducible transcription factors and elicit diverse biological responses in hormone-responsive target tissues. The clinical value of ERAAs stems from their potential to exert favorable effects on hormone-related postmenopausal conditions (eg, reduction in breast cancer, prevention and treatment of osteoporosis, and relief of VVA for some ERAAs) while minimizing unfavorable effects on the urogenital system, endometrium, breast, ovary, bone, and central nervous system. However, a twofold increase in the risk of venous thromboembolism with ERAAs remains a concern for this drug class. The preclinical studies reviewed demonstrate the differential activity of ERAAs in female reproductive and urinary tract tissues and are reasonably predictive of the clinical response of compounds that were successful in clinical trials. Thus, compared with tamoxifen, the less pronounced estrogenic effects of ospemifene, raloxifene, and bazedoxifene on uterine weight and endometrial thickness in animals reflect the endometrial safety profile seen in clinical studies of postmenopausal women. In addition, the increased vaginal epithelial thickness and mucification observed in preclinical studies of ospemifene, but not raloxifene, reflect the improvement in VVA observed in clinical studies of ospemifene. Ospemifene improves vaginal MI and relieves VVA-associated symptoms, unlike raloxifene and bazedoxifene alone. Clinical data on the effects of ERAAs on the breast (other than the effects of tamoxifen and raloxifene), cardiovascular system (including the risk of venous thromboembolism), bone, and brain are not the focus of this article, and available data are reviewed elsewhere[101,107]; characterization of hot flushes with ospemifene will be the topic of a future publication.

Endometrial safety is a major concern with the use of ERAAs in postmenopausal women, and compounds in this class differ in their effects on the endometrium. Raloxifene, bazedoxifene, and ospemifene had no preclinical uterotrophic or negative histologic effects; these findings correlate with their endometrial safety profile in clinical trials. A semisystematic review of controlled studies in which postmenopausal women received raloxifene in combination with systemic estrogens found little evidence of endometrial safety concerns.[108] Tamoxifen, in contrast, has been associated with a pronounced and lasting increase in endometrial thickness, reflecting the relative estrogenic activity identified in preclinical studies, and more importantly increased the risk of endometrial hyperplasia, carcinoma, and ovarian cysts. The combination of specific ERAAs and specific estrogens (whether systemic or vaginal) needs to be tested in large randomized

controlled trials, as effects on tissue may vary from agonist to antagonist, depending on the specific combination and the dose tested.

Limitations of this review include a paucity of preclinical and clinical urodynamic data on the effects of ERAAs on the urinary system. In addition, there are no available data on the effects of combined ospemifene and vaginal or systemic estrogen; however, as ospemifene monotherapy has beneficial effects on VVA, there is little reason to examine this combination. Although ospemifene is a metabolite of toremifene (an ERAA approved for the treatment of hormone-sensitive breast cancer), the use of ospemifene has not been evaluated in populations at high risk for breast or endometrial cancer, nor have potential effects on the bone, breast, and brain tissues been extensively studied; thus, no conclusions can be drawn about efficacy or safety in larger populations.

## CONCLUSIONS

Ospemifene seems to have positive effects on the vagina and neutral effects on the urinary system, compared with the effects of raloxifene, bazedoxifene, and tamoxifen. The relative estrogenic agonist/antagonist activity of each ERAA in specific tissues seems to underlie many of the responses observed in preclinical models, several of which have translated into varying vaginal, endometrial, and urinary tract findings in clinical trials. Ospemifene can be differentiated from other ERAAs that have been approved or that are in late-stage development based on improvements in vaginal morphology, physical changes associated with VVA, and sexual function, and on its favorable endometrial and ovarian safety profile at 52 weeks. Ospemifene is an oral systemic ERAA, with unique effects on VVA, that does not need to be given with vaginal estrogen (unlike raloxifene) or systemic estrogen (unlike bazedoxifene). The unique clinical efficacy and safety profile of ospemifene supports its indication for treating moderate to severe dyspareunia associated with VVA in postmenopausal women. We need more data regarding its effects on other tissues (including the cardiovascular system, bone, breast, and central nervous system) and on vulnerable populations such as women at risk for breast or endometrial cancer.

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