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The evolution of selective estrogen receptor modulators in osteoporosis therapy

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ABSTRACT

Selective estrogen receptor modulators (SERMs), which exhibit estrogen receptor agonist or antagonist activity based on the target tissue, have evolved through multiple generations for the prevention and/or treatment of postmenopausal osteoporosis. An ideal SERM would protect bone without stimulating the breast or endometrium. Raloxifene, lasofoxifene, and bazedoxifene have demonstrated unique preclinical profiles. Raloxifene, lasofoxifene, and bazedoxifene have shown significant reduction in the risk of vertebral fracture and improvement in bone mineral density versus placebo in postmenopausal women with osteoporosis. Raloxifene has been shown to reduce the risk of non-vertebral fractures in women with severe prevalent fractures at baseline. Lasofoxifene 0.5 mg, but not lasofoxifene 0.25 mg, has shown reduction in the incidence of non-vertebral fractures. Bazedoxifene 20 mg has been associated with a significant reduction in the risk of non-vertebral fracture versus placebo and raloxifene 60 mg in women at higher baseline fracture risk. Neither raloxifene, lasofoxifene, nor bazedoxifene has shown an increase in the incidence of endometrial hyperplasia or carcinoma. All SERMs have been associated with increased venous thromboembolic events and hot flushes. SERMs are effective alternatives for women who cannot tolerate or are unwilling to take bisphosphonates and may be appropriate for women at higher risk of fracture, particularly younger women who expect to remain on therapy for many years and are concerned about the long-term safety of bisphosphonates.

INTRODUCTION

Selective estrogen receptor modulators (SERMs) have been found to be effective pharmacological interventions for the management of a variety of diseases related to estrogen deficiency in postmenopausal women[1]. SERMs bind to estrogen receptors (ER) α and β and have agonist or antagonist activity depending on the compound itself as well as the target tissue[2,3]. ERα and ERβ are disproportionally distributed in the brain[4], uterus[5], bone[6,7], breast[5], ovary[5], and liver[8] (Figure 1). Based on this varied distribution of ERs, an optimally designed SERM would exhibit beneficial effects on the skeleton, cardiovascular system (e.g. lipid profile), and central nervous system (e.g. vasomotor effects), without having adverse effects on the endometrium or breast[2].

Tamoxifen, a first-generation SERM, exhibits ER antagonist activity in the breast and is considered the first-line treatment for ER-positive breast cancer in premenopausal women[9]. It has also been shown to be effective in preventing breast cancer in women regardless of age[10,11]. However, an analysis of data from the Breast Cancer Prevention Trial indicated that the risks of endometrial cancer, stroke, pulmonary embolism, and deep vein thrombosis associated with tamoxifen were elevated in women aged 50 years and older[11], suggesting that the side-effect profile of tamoxifen may not be appropriate for breast cancer prevention, especially in older postmenopausal women[12].

Tamoxifen has demonstrated ER agonist activity in the skeleton, with favorable effects on bone mineral density (BMD) in postmenopausal women (a decrease in BMD has been seen in premenopausal women)[13]. Tamoxifen has been shown to significantly reduce the overall risk of fracture in postmenopausal women with osteoporosis and reduce the risk of hip fracture in women aged ≥ 50 years with a first osteoporotic fracture[14]. It has also been shown to decrease low density lipoprotein (LDL) cholesterol[10] and the risk of

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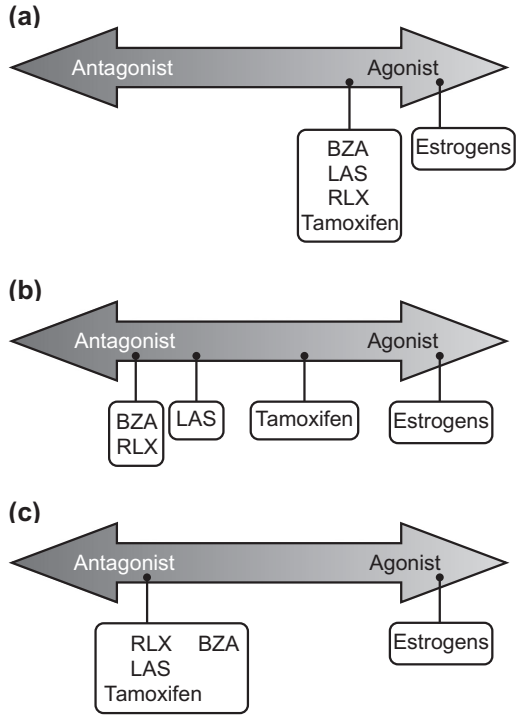

Figure 1 Relative agonist and antagonist activities of selective estrogen receptor modulators (SERMs) in different target tissues: (a) bone, (b) endometrium, (c) breast. BZA, bazedoxifene; LAS, lasofoxifene; RLX, raloxifene

cardiovascular disease[9]. Tamoxifen exhibits ER agonist activity in the uterus and is associated with an increased risk of endometrial cancer[10,15].

Raloxifene (RLX) is the best characterized example of a second-generation SERM[10]. It is approved for prevention and treatment of postmenopausal osteoporosis in the Unites States and European Union and for the prevention of breast cancer in the United States[16,17]. In a recent combined analysis of multiple clinical trials that evaluated RLX and tamoxifen for the prevention of invasive breast cancer, benefit/risk indices were constructed for risk groups based on factors such as age, ethnicity, breast cancer risk, and the presence of a uterus. For RLX versus tamoxifen, there were more groups with stronger evidence that the benefits of treatment outweigh its risks in postmenopausal women over 50 years of age with a uterus[12]. Additionally, long-term use of RLX was associated with a significant decrease in all-cause mortality compared with placebo ($p = 0.05$) in a pooled analysis of data from studies among older postmenopausal women[18].

The third-generation SERMs, lasofoxifene (LAS) and bazedoxifene (BZA), are approved in the European Union for the treatment of postmenopausal osteoporosis in women at increased risk of fracture[10,19,20]. This article summarizes how SERMs have evolved in osteoporosis treatment and discusses the molecular details of how SERMs exert their bone-sparing effects. The key clinical trial results with SERMs developed for the management of osteoporosis will also be reviewed.

SERMs: MECHANISM OF ACTION

Upon ligand binding, ERs adopt different conformations and spontaneously dimerize. Once dimerized, the ER complex becomes capable of modulating gene transcription[21]. This modulation can occur through agonist or antagonist binding to the ER complex. Agonist binding recruits coactivators to the ER complex, which triggers gene transcription, while antagonist binding recruits corepressors to the ER complex, which prevents transcription[21].

It has been shown that SERMs elicit different gene expression profiles from one another and, in some tissues, from estrogens[22]. The SERM–ER complex structure differs from that attained with traditional agonists or antagonists, based on characteristics of the SERM[23]. Individual SERM–ER complexes have distinct activities in different tissues[21]. Similar to estrogens, SERMs generally function as agonists in bone[21] through the activity of osteoclasts and osteoblasts, and may be considered to have a more physiologic mechanism of action compared with other pharmacologic agents (e.g. bisphosphonates). SERMs have been shown to directly decrease osteoclast differentiation and bone resorption activity, while stimulating osteoblast activity and proliferation in bone marrow cultures from neonatal mice[24]. SERMs may also increase the activity of osteoblasts by stimulating osteoprotegerin expression and decreasing nuclear factor-κB ligand (RANKL) levels. Lower ratios of RANKL to osteoprotegerin have been associated with increased osteoblastic activity and preservation of BMD[25].

PRECLINICAL EVALUATION OF SERMs

Raloxifene

In an ovariectomized (OVX) rat model, treatment with RLX 3.0 mg/kg/day for 6 months was associated with significant increases in lumbar vertebral and proximal tibia BMD ($p < 0.001$ for both) and significant increases in lumbar vertebral ($p < 0.05$) and femoral neck ($p < 0.01$) bone strength compared with OVX controls[26]. Treatment of OVX rats with RLX 0.1–1.0 mg/kg/day for 6 months showed a significant increase in uterine wet weight ($p < 0.05$), but uterine histology did not differ from control[27]. RLX has been shown to prevent the development of mammary tumors during 4.5 months of treatment in rats, with a reduction in incidence of 55% and 57% ($p < 0.001$ for both) compared with placebo for RLX 60 and 20 mg/day, respectively[28].

Lasofoxifene

LAS 60, 150, and 300 μg/kg/day prevented ovariectomy-induced reductions in BMD through 1 year of treatment in OVX rats and significantly increased the ultimate strength of the L4 lumbar vertebra by 37%, 40%, and 47%, respectively, compared with control ($p < 0.05$)[29]. These doses of LAS were

associated with a significant increase in uterine wet weight (16%, 20%, and 11% for LAS 60, 150, and 300 μg/kg/day, respectively) compared with control ($p < 0.05$); there were no significant changes in uterine histology[29]. In a rat model of *N*-nitroso-*N*-methylurea-induced mammary tumors, treatment with LAS 0.1–10 mg/kg/day for 8 weeks delayed the formation of mammary tumors by 17–32 days compared with vehicle control[30].

Bazedoxifene

In OVX rats, treatment with BZA 0.1, 0.3, 1.0, and 3.0 mg/kg/day for 6 weeks showed significant, dose-dependent increases in BMD ($p < 0.01$ vs. OVX control) and increased compressive strength of the L4 vertebra ($p \leq 0.05$) compared with vehicle control[3,31]. After treatment with BZA 3.0 mg/kg/day for 6 weeks, uterine wet weights of OVX rats were not different compared with vehicle control[31]. Similarly, OVX rats treated with BZA 0.3 mg/kg/day for 1 year showed uterine wet weights that were not different from those of OVX control rats[32]. BZA did not induce proliferation of the MCF-7 breast cancer cell line during 7 days of treatment[3]. In OVX mice treated for 7 days with BZA 3.0 mg/kg/day, BZA did not stimulate breast tissue, as measured by mammary gland end bud formation[33]. In an OVX sexually immature mouse model, treatment with BZA 2.0 mg/kg/day for 14 days resulted in ductal branch point invasion that was not different from that with vehicle control ($p > 0.05$)[34].

Preclinical comparison of SERMs

Several studies have been conducted to compare the preclinical profile of second- and third-generation SERMs such as RLX, LAS, and BZA. In OVX rats, the effects of BZA 0.3 mg/kg/day for 6 weeks on BMD, histomorphometry, and total cholesterol were comparable to those with RLX 3.0 mg/kg/day[3]. Uterine and mammary gland responses to treatment with different SERMs were evaluated after 7 days in a study of OVX mice[33]. Treatment with RLX, LAS, and BZA at a dose of 3.0 mg/kg/day showed small increases in uterine wet weight versus vehicle control ($p < 0.05$), with the smallest increase for BZA (44%) compared with RLX (79%) or LAS (217%)[33]. Consistent with what was seen with BZA, RLX and LAS did not stimulate breast tissue, as measured by mammary gland end bud formation[33]. BZA and RLX, but not LAS, were shown to reverse estradiol-induced terminal end bud formation[33].

In an OVX sexually immature mouse model, the minimum doses of RLX, LAS, and BZA that were required to maximally inhibit conjugated estrogen (CE)-induced increases in uterine wet weight were determined (10 mg/kg/day for RLX, 2 mg/kg/day for LAS, and 2 mg/kg/day for BZA), and the effects of these SERMs on uterine and mammary tissue were evaluated over 14 days of treatment[34]. Uterine wet weights increased compared with vehicle control in the order LAS 2 mg/kg/day $<$ RLX 10 mg/kg/day $<$ BZA 2 mg/kg/day, with significant differences ($p < 0.05$) between groups[34]. BZA 2 mg/kg/day and RLX 10 mg/kg/day were more effective at antagonizing CE-induced uterine stimulation than LAS 2 mg/kg/day[34]. In the mammary gland, treatment with BZA 2 mg/kg/day was associated with lower amphiregulin mRNA expression, a measure of mammary gland ER agonist activity, compared with RLX 10 mg/kg/day or LAS 2 mg/kg/day ($p < 0.05$ for the difference between each group)[34]. In the mammary gland whole mount assay, BZA 2 mg/kg/day and RLX 10 mg/kg/day, but not LAS 2 mg/kg/day, had a similar number of ductal branch points as vehicle control[34]. BZA 2 mg/kg/day was more effective than RLX 10 mg/kg/day or LAS 2 mg/kg/day at preventing ductal tree fat pad invasion ($p < 0.05$ for both comparisons)[34].

The effects of different SERMs (BZA, 4-hydroxytamoxifen, endoxifen, RLX) and the pure antiestrogen fulvestrant on the proliferation of hormone-dependent and -independent breast cancer cells were evaluated[35]. Using protein expression assays and molecular modeling studies of the binding of each SERM to ERα, BZA was shown to inhibit hormone-dependent cell growth and to regulate ERα and cyclin D1 in hormone-independent cells in a manner distinct from all of the other SERMs[35]. Gene expression profiling has shown different patterns of gene expression for BZA, RLX, and LAS, with more similarity between RLX and BZA than between either of these agents and LAS[36]. The results of these studies indicate that SERMs have distinct preclinical profiles. The doses required to achieve similar bone-protective effects vary as much as 10-fold among SERMs[2,3], and the ER agonist and antagonist profiles in uterine and breast tissue also differ among SERMs[33,34].

CLINICAL TRIALS OF SERMs

RLX, LAS, and BZA have each been evaluated in phase-3 clinical trials conducted in postmenopausal women with osteoporosis.

Raloxifene

The phase-3, Multiple Outcomes of Raloxifene Evaluation (MORE) trial evaluated RLX 60 and 120 mg/day for 3 years in 7705 postmenopausal women with osteoporosis[37,38]. The Continuing Outcomes Relevant to Evista (CORE) trial was a 4-year extension study that enrolled 4011 women who were previously enrolled in the MORE trial[39,40]. In the CORE trial, women who had received RLX 60 and 120 mg during the MORE trial were all given RLX 60 mg, and women who had received placebo continued to do so.

At 3 years, RLX 60 and 120 mg reduced the incidence of new vertebral fractures by 30% (relative risk (RR) 0.7; 95% confidence interval (CI) 0.5–0.8) and 50% (RR 0.5; 95% CI 0.4–0.7), respectively, versus placebo in the MORE trial (Table 1)[37]. The risk of non-vertebral fracture was similar

Table 1 Bone effects of SERMs in phase-3 treatment studies

	Raloxifene (MORE; $n = 7705$)[37], (CORE; $n = 4011$)[41]		*Lasofoxifene* (PEARL; $n = 8556$)[47,76]		*Bazedoxifene* ($n = 7492$ and $n = 4216$)[51,56]	
	60 mg	*120 mg*	*0.25 mg*	*0.5 mg*	*20 mg*	*40 mg*
Vertebral fracture risk reduction (%)*						
3 years	30% (RR 0.7; 95% CI 0.5–0.8)	50% (RR 0.5; 95% CI 0.4–0.7)	31%† (HR 0.69; 95% CI 0.55–0.87)	42%‡ (HR 0.58; 95% CI 0.45–0.73)	42%** (HR 0.58; 95% CI 0.38–0.89)	37%** (HR 0.63; 95% CI 0.42–0.96)
5 years	–	–	31%‡ (HR 0.69; 95% CI 0.57–0.83)	42%‡ (HR 0.58; 95% CI 0.47–0.70)	35% (HR 0.65; 95% CI 0.46–0.91)	–
Non-vertebral fracture risk reduction (%)*						
3 years	10% (RR 0.9; 95% CI 0.8–1.1 for pooled RLX 60/120 mg)		–	–	40%** (HR 0.60; 95% CI 0.37–0.95 for pooled BZA 20/40 mg in a *post hoc* analysis of subjects at higher risk of fracture)	
5 years	–	–	10% (HR 0.90; 95% CI 0.76–1.06)	24%† (HR 0.76; 95% CI 0.64–0.91)	31% (HR 0.69; 95% CI 0.42–1.13 for pooled BZA 20/40 mg in a *post hoc* analysis of subjects at higher risk of fracture)	
8 years	0% (RR 1.0; 95% CI 0.8–1.2 for pooled RLX 60/120 mg)		–	–	–	
Mean change from baseline in lumbar spine BMD (%)						
3 years	2.6%‡	2.7%‡	–	–	2.2%‡	2.4%‡
5 years	–	–	3.0%†† (95% CI 2.6–3.3%) vs. placebo	3.1%†† (95% CI 2.8–3.5%) vs. placebo	2.1%‡ for pooled BZA 20/40 mg	
7 years	4.3%‡ for pooled RLX 60/120 mg		–	–	–	–
Median change from baseline in urinary C-telopeptide (%)						
1 year	–	–	−48% (95% CI −51 to −45%)	−53% (95% CI −55 to −48%)	−46%‡	−49%‡
3 years	−34.0%‡	−31.5%‡	–	–	–	–
Median change from baseline in serum osteocalcin (%)						
1 year	–	–	−45% (95% CI −47 to −44%)	−46% (95% CI −50 to −43%)	−37%‡	−39%‡
3 years	−26.3%‡	31.1%‡	–	–	–	–

SERM, selective estrogen receptor modulator; MORE, Multiple Outcomes of Raloxifene Evaluation; CORE, Continuing Outcomes Relevant to Evista; PEARL, Postmenopausal Evaluation And Risk-reduction with Lasofoxifene; RR, relative risk; CI, confidence interval; HR, hazard ratio; RLX, raloxifene; BZA, bazedoxifene; BMD, bone mineral density
*, HR and RR versus placebo; †, $p < 0.01$ vs. placebo; ‡, $p < 0.001$ vs. placebo; **, $p < 0.05$ vs. placebo; ††, % reduction vs. placebo (not vs. baseline)

among the RLX and placebo groups at 3 years in the MORE trial[37] and at 8 years in the CORE trial[41]. In a reanalysis of data from women enrolled in the MORE study who did not have baseline vertebral fractures ($n = 3204$)[42], RLX 60 mg was shown to reduce the risk of vertebral fractures and all clinical fractures in women with osteoporosis or osteopenia as defined by baseline hip BMD based on the Third National Health and Nutrition Examination Survey (NHANES III) database. In a *post hoc* secondary analysis of data from women enrolled in the MORE trial with the most severe prevalent vertebral fractures at baseline (semiquantitative assessment = 3; $n = 614$), RLX 60 mg was associated with a significantly decreased risk of non-vertebral fracture at 3 years ($p = 0.046$)[43].

Relative to placebo, lumbar spine BMD values were increased by 2.6% for RLX 60 mg and by 2.7% for RLX 120 mg ($p < 0.001$) at 3 years[37]. BMD changes were evaluated at 7 years in a substudy of the CORE study. Lumbar spine BMD values were increased by 2.2% in the pooled RLX 60/120 mg group compared with placebo ($p < 0.01$)[41].

Hot flushes were more common in women taking RLX compared with placebo ($p < 0.001$) over 8 years of treatment in the MORE and CORE trials[40].

The Raloxifene Use for The Heart (RUTH) trial investigated the effects of RLX 60 mg in a population of postmenopausal women with cardiac heart disease or risk factors for cardiac heart disease ($n = 10\,101$)[44]. After a median follow-up of

5.6 years, there was no significant difference between RLX 60 mg and placebo in the risk of primary coronary events, including death from coronary causes, myocardial infarction, or hospitalization for an acute coronary syndrome other than myocardial infarction (hazard ratio (HR) 0.95; 95% CI 0.84–1.07). The risk of invasive breast cancer in this trial was lower for RLX 60 mg than for placebo (HR 0.56; 95% CI 0.38–0.83; absolute risk reduction, 1.2 invasive breast cancers per 1000 women)[44]. There was no significant difference among groups in the overall risk of stroke in the RUTH trial, although RLX 60 mg was associated with an increased risk of fatal stroke compared with placebo (HR 1.49; 95% CI 1.00–2.24; Table 2)[44].

For subjects in the MORE trial, the risk of venous thromboembolism (VTE) was higher with both doses of RLX (60 and 120 mg combined) than with placebo (RR 3.1; 95% CI 1.5–6.2; Table 2)[37]. In an 8-year safety evaluation of the MORE and CORE studies, the risk of VTE was determined to be 1.7 times higher with RLX 60/120 mg combined than with placebo. There was no significant difference in the total incidence of stroke between RLX 60/120 mg and placebo[40].

Lipid effects from the MORE trial were not reported, but in a 2-year, multicenter, double-blind, placebo-controlled study of postmenopausal women with normal or low BMD ($n = 601$), RLX 60 mg was associated with a significant decrease from baseline in total and LDL cholesterol ($p < 0.05$ vs. placebo) and with no significant changes from baseline in high density lipoprotein (HDL) cholesterol or triglycerides (Table 3)[45].

Over 4 years of treatment in the MORE trial, there were no significant differences between RLX 60 or 120 mg or placebo in the incidence of endometrial hyperplasia or carcinoma (Table 4)[38]. Endometrial thickness increased by 0.01 mm for women taking RLX 60 mg and decreased by 0.27 mm for women taking placebo ($p < 0.01$ vs. placebo)[38]. The incidence of endometrial polyps was higher in the RLX groups than in the placebo group ($p = 0.028$) at 8 years in the MORE and CORE trials[40]. In the MORE trial, the overall incidence of breast cancer was significantly reduced with both doses of RLX combined versus placebo (RR 0.4; 95% CI 0.2–0.6; $p < 0.001$)[38]. In the CORE trial, RLX 60 mg reduced the incidence of invasive breast cancer and ER-positive breast cancer by 59% and by 66%, respectively[39]. RLX has been shown to be as effective as tamoxifen in preventing invasive breast cancer in postmenopausal women in the Study of Tamoxifen And Raloxifene (STAR) trial ($n = 19\,747$)[46], but with a more favorable benefit/risk ratio for postmenopausal women with a uterus (Table 4)[12].

Lasofoxifene

LAS 0.25 and 0.5 mg/day were evaluated in the phase-3, 5-year, Postmenopausal Evaluation and Risk-reduction with Lasofoxifene (PEARL) trial ($n = 8556$)[47]. PEARL enrolled postmenopausal women aged 59–80 years with osteoporosis, defined as a lumbar spine or femoral neck BMD *T*-score of ≤ -2.5.

Daily treatment over 3 years with LAS 0.25 and 0.5 mg was associated with significant reductions of 31% (HR 0.69; 95% CI 0.55–0.87) and 42% (HR 0.58; 95% CI 0.45–0.73), respectively, in the risk of vertebral fracture compared with placebo ($p < 0.01$ for both). The significant reductions in vertebral fracture risk were maintained at 5 years ($p < 0.001$ for both; Table 1)[47]. LAS 0.5 mg (but not LAS 0.25 mg) also reduced the risk of non-vertebral fracture versus placebo at 5 years ($p = 0.002$ for LAS 0.5 mg)[47].

Relative to placebo, lumbar spine BMD improved at 5 years in the PEARL trial by 3.0% with LAS 0.25 mg and by 3.1% with LAS 0.5 mg (Table 1)[47].

More women reported hot flushes in the LAS groups ($n = 372$ (13.0%) and $n = 365$ (12.8%) for LAS 0.25 and 0.5 mg, respectively) than in the placebo group ($n = 158$ (5.5%); $p < 0.001$ for both) over 5 years of treatment[47].

Table 2 Cardiovascular safety profiles of SERMs in phase-3 treatment studies

	Raloxifene (MORE; $n = 7705$)[38], (RUTH; $n = 10\,101$)[44]		*Lasofoxifene* (PEARL; $n = 8556$)[48]		*Bazedoxifene* ($n = 7492$ and $n = 4216$)[54,58]	
	60 mg	*120 mg*	*0.25 mg*	*0.5 mg*	*20 mg*	*40 mg*
*Incidence of venous thromboembolism**						
3 years	RR 3.1 (95% CI 1.5–6.2) for pooled RLX 60/120 mg		–	–	HR† 1.6 (95% CI 0.68–3.94)	HR† 1.7 (95% CI 0.79–4.07)
5 years	–	–	HR 2.67‡ (95% CI 1.55–4.58)	HR 2.06** (95% CI 1.17–3.61)	HR† 1.5 (95% CI 0.68–3.35)	–
Incidence of total stroke						
3 years	–	–	–	–	HR† 0.9 (95% CI 0.40–1.86)	HR† 1.0 (95% CI 0.49–2.17)
5 years	HR 1.10 (95% CI 0.92–1.32)	–	HR 0.61 (95% CI 0.39–0.96)	HR 0.64 (95% CI 0.41–0.99)	HR† 0.8 (95% CI 0.43–1.63)	–

SERM, selective estrogen receptor modulator; MORE, Multiple Outcomes of Raloxifene Evaluation; RUTH, Raloxifene Use for The Heart (phase-3 cardiovascular effects study); PEARL, Postmenopausal Evaluation And Risk-reduction with Lasofoxifene; RR, relative risk; RLX, raloxifene; HR, hazard ratio; CI, confidence interval

*, HR and RR versus placebo; †, adjudicated data; ‡, $p = 0.001$ vs. placebo; **, $p = 0.01$ vs. placebo

Table 3 Lipid effects. Data are given as median (standard error) percent change from baseline

	Raloxifene Phase-3 prevention study ($n = 601$)[45]		*Lasofoxifene Phase-3 treatment study* (PEARL; $n = 8556$)[47]		*Bazedoxifene Phase-3 treatment study* ($n = 7492$)[54]	
	60 mg	*120 mg*	*0.25 mg*	*0.5 mg*	*20 mg*	*40 mg*
Total cholesterol						
2 years	−6.4 (1.1)*	–	–	–	–	–
3 years	–	–	–	–	−3.8†	−3.5†
LDL cholesterol						
2 years	−10.1 (1.4)*	–	–	–	–	–
3 years	–	–	−16.2% (95% CI −19.7 to −12.7%)	−15.8% (95% CI −19.5 to −12.0%)	−5.4†	−6.6†
HDL cholesterol						
2 years	−3.7 (0.8)	–	–	–	–	–
3 years	–	–	no significant effects	no significant effects	5.1†	5.9†
Triglycerides						
2 years	3.2 (3.1)	–	–	–	–	–
3 years	–	–	8.0% (95% CI 1.5–14.6%)	4.9% (95% CI −2.2 to 11.9%)	8.5	13.6

PEARL, Postmenopausal Evaluation And Risk-reduction with Lasofoxifene; LDL, low density lipoprotein; CI, confidence interval; HDL, high density lipoprotein

*, $p < 0.05$ vs. placebo; †, $p < 0.001$ vs. placebo

An increased risk of VTE was seen with LAS 0.25 mg (HR 2.67; 95% CI 1.55–4.58) and LAS 0.5 mg (HR 2.06; 95% CI 1.17–3.61) compared with placebo ($p = 0.01$ and $p < 0.001$, respectively) at 5 years (Table 2)[48]. In the same study, LAS 0.25 mg (HR 0.61; 95% CI 0.39–0.96) and LAS 0.5 mg (HR 0.64; 95% CI 0.41–0.99) decreased the risk of stroke compared with placebo. The risk of major coronary heart disease events was reduced by 32% with LAS 0.5 mg compared with placebo (HR 0.68; 95% CI 0.50–0.93; $p = 0.02$); the 24% decrease seen with LAS 0.25 mg was not statistically significant compared with placebo (HR 0.76; 95% CI 0.58–1.03; $p = 0.08$)[48].

Three years of treatment with LAS did not affect HDL cholesterol but was associated with a reduction in LDL cholesterol for LAS 0.25 and 0.5 mg. LAS 0.25 and 0.5 mg were associated with increases in triglycerides at 3 years (Table 3)[47].

There was a statistically significant increase in endometrial thickness from baseline for women treated with LAS 0.25 mg (1.19 mm) and LAS 0.5 mg (1.43 mg; $p < 0.001$ vs. placebo), although the incidences of endometrial hyperplasia and endometrial carcinoma were not significantly different for LAS compared with placebo (Table 4)[49]. A significantly higher proportion of women in the LAS 0.25-mg (7.2%) and LAS 0.5-mg (7.0%) groups required diagnostic uterine procedures based on clinical trial protocol requirements for reports of vaginal bleeding or transvaginal ultrasound abnormalities compared with those in the placebo group (2.7%; $p = 0.001$)[47,49]. The incidence of uterine polyps was significantly higher with LAS 0.25 and 0.5 mg compared with placebo ($p < 0.001$ for both); based on histologic results, all polyps seen in the LAS groups were associated with atrophic features[49]. Overall, LAS 0.5 mg showed a 79% reduced risk of breast cancer versus placebo; the reduction in breast cancer risk was not significantly different between placebo and LAS 0.25 mg[50]. LAS 0.5 mg was associated with an 85% reduced risk of invasive breast cancer versus placebo ($p < 0.001$)[47]. Although there was no difference in mortality between LAS 0.5 mg and placebo in the PEARL trial, there was a statistically significant increase in mortality with LAS 0.25 mg (90 deaths, 3.2%, 7.0 deaths per 1000 person-years) compared with placebo (65 deaths, 2.3%, 5.1 deaths per 1000 person-years; $p = 0.05$). There was a trend toward more deaths due to cancer with LAS 0.25 mg (34 cases, 1.2%) than with placebo (20 cases, 0.7%; $p = 0.06$)[47].

Bazedoxifene

The pivotal phase-3 treatment study of BZA 20 and 40 mg/day versus RLX 60 mg and placebo was conducted in healthy postmenopausal women aged 55–85 years ($n = 7492$) with osteoporosis over 3 years[51]. Osteoporosis was defined as lumbar spine or femoral neck *T*-score between −2.5 and −4.0 for women without prevalent vertebral fracture, or *T*-score ≥ -4.0 for women with prevalent vertebral fracture.

The incidence of new vertebral fractures with BZA 20 and 40 mg was significantly reduced by 42% (HR 0.58; 95% CI 0.38–0.89) and 37% (HR 0.63; 95% CI 0.42–0.96), respectively, and by 42% (HR 0.58; 95% CI 0.38–0.89) with RLX 60 mg compared with placebo ($p < 0.05$ for all; Table 1)[51]. There were no overall significant differences between BZA 20 or 40 mg, RLX 60 mg, or placebo in the incidence of non-vertebral fractures[51]. However, in a *post hoc* analysis of a subgroup of higher-risk women (baseline femoral neck BMD *T*-score ≤ -3.0 and/or ≥ 1 moderate or severe vertebral fracture or ≥ 2 mild fractures; $n = 1772$), BZA 20 mg was

Table 4 Incidence of endometrial and breast-related adverse events in phase-3 treatment studies of SERMs

	Raloxifene (MORE; $n = 7705$)[38], (CORE; $n = 4011$)[40]		*Lasofoxifene* PEARL ($n = 8556$)[47,49,50]		*Bazedoxifene* ($n = 7492$ and $n = 4216$)[54,58]	
	60 mg	*120 mg*	*0.25 mg*	*0.5 mg*	*20 mg*	*40 mg*
Endometrial safety						
Incidence of endometrial hyperplasia						
3 years	0.05% (for pooled RLX 60/120 mg)		–	–	0.1%	0.1%
5 years	–	–	0.11%	0.07%	0.1%	–
Incidence of endometrial cancer						
3 years	0.2%	<0.1%	–	–	0	0.1%
5 years	–	–	0.07%	0.07%	0	–
Incidence of endometrial neoplasia (polyps)						
3 years	–	–	–	–	0.5%	0.6%
5 years	–	–	3.8%*	4.0%*	0.7%	–
8 years	3.2%†					
Change from baseline in endometrial thickness (mm)						
2 years			–	–	-0.07 ± 0.11	0.10 ± 0.12
3 years	0.01** (for pooled RLX 60/120 mg)		–	–	–	–
5 years	–	–	1.19*	1.43*	-0.05 ± 0.13	–
Breast safety						
Overall incidence of breast cancer‡						
3 years	RR vs. placebo 0.35* (95% CI 0.21–0.58) for pooled RLX 60/120 mg		–	–	0.3%	0.2%
5 years	–	–	0.73% (HR vs. placebo 0.82; 95% CI 0.45–1.49)	0.18% (HR vs. placebo 0.21*; 95% CI 0.08–0.55)	0.5%**	–
Incidence of ER-positive breast cancer‡						
3 years	0.08% (RR vs. placebo 0.10; 95% CI 0.04–0.24 for pooled RLX 60/120 mg)		–	–	–	–
5 years	–	–	0.40% (HR vs. placebo 0.52; 95% CI 0.25–1.08)	0.15% (HR vs. placebo 0.19*; 95% CI 0.07–0.56)	–	–
Incidence of invasive breast cancer‡						
3 years	0.25% (RR vs. placebo 0.24; 95% CI 0.13–0.44 for pooled RLX 60/120 mg)		–	–	–	–
5 years	–	–	0.59% (HR vs. placebo 0.79; 95% CI 0.41–1.52)	0.11% (HR vs. placebo 0.15*; 95% CI 0.04–0.50)	0.5%	–

SERM, selective estrogen receptor modulator; MORE, Multiple Outcomes of Raloxifene Evaluation; CORE, Continuing Outcomes Relevant to Evista; PEARL, Postmenopausal Evaluation And Risk-reduction with Lasofoxifene; RLX, raloxifene; RR, relative risk; CI, confidence interval; HR, hazard ratio; ER, estrogen receptor
*, $p \leq 0.001$ vs. placebo; †, $p < 0.05$ vs. placebo; ‡, RR and HR vs. placebo; **, $p < 0.01$ vs. placebo

associated with a 50% reduction in non-vertebral fracture risk versus placebo ($p = 0.02$) and a 44% reduction versus RLX 60 mg ($p = 0.05$)[51]. The fracture data from the overall population were independently re-evaluated based on baseline fracture risk using the Fracture Risk Assessment Tool (FRAX®)[52,53]. Consistent with the results of the original *post hoc* subgroup analysis, the efficacy of BZA on non-vertebral, morphometric, and all clinical fractures was shown to increase with an increasing likelihood of fractures[52,53]. Specifically, BZA (based on combined data for the 20- and 40-mg doses) significantly decreased the risk of morphometric vertebral, clinical, and non-vertebral fractures for women at or above the 6.9%, 16.0%, and 20.0% probability thresholds, respectively[52,53]. These results suggest that women at higher risk of fracture are most likely to benefit from treatment with BZA[52].

BZA 20 and 40 mg and RLX 60 mg significantly improved changes in lumbar spine BMD from baseline by 2.21%, 2.38%, and 2.96%, respectively, compared with placebo (0.88%; $p < 0.001$ vs. placebo for all) at 3 years (Table 1)[51].

BZA 20 and 40 mg were generally safe and well tolerated, with an overall safety profile similar to those with RLX 60 mg and placebo[51,54]. The incidence of hot flushes was greater for

women treated with BZA 20 mg (12.6%), BZA 40 mg (13.0%), and RLX 60 mg (12.0%) compared with placebo (6.3%; overall $p < 0.001$)[51].

The incidence of cardiovascular adverse events was generally low among groups[51,54]. There was a higher incidence of VTE with BZA 20 mg (HR 1.6; 95% CI 0.8–3.94), BZA 40 mg (HR 1.7; 95% CI 0.70–4.07), and RLX 60 mg (HR 1.1; 95% CI 0.44–2.96) compared with placebo, primarily due to deep vein thromboses (Table 2). There was no difference in the incidence of stroke between placebo and BZA 20 and 40 mg or RLX 60 mg[54].

The reductions from baseline in total and LDL cholesterol for BZA 20 and 40 mg and RLX 60 mg were significantly greater compared with placebo ($p < 0.001$ for all; Table 3). There were significant increases from baseline in HDL cholesterol for BZA 20 and 40 mg and RLX 60 mg compared with placebo ($p < 0.001$) and no significant differences between groups in changes from baseline in triglycerides[54].

There were no significant differences in the incidence of endometrial hyperplasia or endometrial carcinoma among treatment groups (Table 4). At 1 year, there was a significant increase from baseline in endometrial thickness for RLX 60 mg (0.32 mm) compared with placebo (−0.11 mm; $p = 0.010$), which was not seen with BZA 20 mg (0.11 mm) or BZA 40 mg (−0.01 mm)[55]. There were no significant differences from baseline in endometrial thickness for BZA 20 or 40 mg, RLX 60 mg, or placebo at 2 years[51,54]. The incidence of endometrial neoplasia (polyps) was not significantly different for BZA 20 or 40 mg, RLX 60 mg, or placebo at 3 years[54]. There were numerically fewer cases of breast cancer in the BZA groups ($n = 6$ for BZA 20 mg and $n = 4$ for BZA 40 mg) than in the RLX 60 mg group ($n = 7$) or the placebo group ($n = 8$); the differences were not statistically significant[54,55].

In a 2-year extension ($n = 4216$) of the core treatment study (years 4–5), the RLX 60-mg arm was discontinued and subjects receiving BZA 40 mg were transitioned to BZA 20 mg (BZA 40/20 mg) during year 4. In a second 2-year extension (years 6–7; $n = 1732$), all subjects continued to receive BZA 20 mg or placebo[56,57]. The efficacy of BZA 20 mg on vertebral fractures was sustained through 5 and 7 years[56,57]. At 5 years, the risk of new vertebral fracture was reduced by 35% and 40% compared with placebo for BZA 20 mg and BZA 40/20 mg, respectively ($p < 0.05$ vs. placebo for both)[56]. Non-vertebral fracture incidence was not different among groups in the overall population at 5 or 7 years. In the higher-risk subgroup, the reduction in the risk of non-vertebral fracture with BZA 20 mg was 37% versus placebo ($p = 0.06$) at 5 years; combined BZA data showed a 34% reduction versus placebo ($p = 0.05$)[56]. The safety and tolerability profiles of BZA at 5 and 7 years were generally consistent with those at 3 years[57,58].

Bazedoxifene/conjugated estrogens

BZA paired with CE is a tissue selective estrogen complex being evaluated for the treatment of menopausal symptoms and the prevention of postmenopausal osteoporosis. In the 2-year, phase-3, Selective estrogens, Menopause, And Response to Therapy (SMART)-1 trial ($n = 3397$)[59–62] of postmenopausal women with a uterus, BZA 20 mg/CE 0.45 and 0.625 mg significantly increased lumbar spine BMD and reduced bone turnover marker levels compared with placebo ($p < 0.001$ for all) and showed low rates of endometrial hyperplasia in postmenopausal women with a uterus[59,61]. In subgroups of symptomatic women, BZA 20 mg/CE 0.45 and 0.625 mg significantly reduced the number and severity of hot flushes and improved measures of vulvar/vaginal atrophy[60]. BZA 20 mg/CE 0.45 and 0.625 mg have also been associated with high rates of amenorrhea[62]. In a larger study of symptomatic postmenopausal women with moderate-to-severe hot flushes (SMART-2; $n = 318$), BZA 20 mg/CE 0.45 and 0.625 mg significantly reduced the number and severity of hot flushes over 12 weeks[63]. BZA 20 mg/CE 0.45 and 0.625 mg were also effective in treating postmenopausal women with moderate-to-severe vulvar/vaginal atrophy over 12 weeks (SMART-3; $n = 652$)[64]. In all three SMART trials, the incidences of adverse events were low and similar between BZA/CE and placebo[60,63,64].

THE ROLE OF SERMs IN THE PREVENTION AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

Currently approved pharmacologic treatment options for osteoporosis include bisphosphonates, hormone therapy, parathyroid hormone, calcitonin, strontium ranelate (outside of North America), denosumab, and SERMs[65–67]. Bisphosphonates are considered the first-line treatment for postmenopausal osteoporosis, with demonstrated efficacy in reducing the incidence of vertebral fracture and, for risedronate and zoledronic acid, non-vertebral fracture[65]. Bisphosphonates have also shown significant improvements in BMD of the spine and hip[65]. However, bisphosphonates may be associated with safety and tolerability issues such as gastrointestinal intolerability (oral formulations)[68] and acute-phase reaction symptoms (intravenous formulations)[69,70]. Concerns related to long-term treatment include the potential for atypical fractures[71], risk of osteonecrosis of the jaw[72–74], and excessive suppression of bone turnover[75]. In contrast to bisphosphonates that inhibit osteoclast activity[75], SERMs behave similar to estrogens in bone and may therefore be considered to be more physiological in action. SERMs may be an appropriate option for women who cannot tolerate bisphosphonates or for younger women at higher risk of fracture who will be treated for many years and are concerned about the long-term safety of bisphosphonates. The combination of SERMs and estrogens may be an option for women at increased risk of fracture who are still experiencing vasomotor symptoms. Sequential treatment for osteoporosis may be individualized by using both a SERM and a bisphosphonate at different points throughout a woman's lifetime. For such a treatment strategy, the well-established, long-term safety profile of SERMs (8 years of follow-up for RLX, 7 years of follow-up for BZA) is reassuring.

CONCLUSIONS

Over the years, SERMs have evolved toward the goal of an 'ideal' SERM, an agent that has positive effects on the skeleton, cardiovascular system (e.g. lipid profile), and central nervous system without stimulation of breast or uterine tissue. The preclinical profiles of individual SERMs demonstrate variable effects on bone, uterine tissue, and breast tissue. BZA has been shown to be effective in preserving bone mass at low doses[3]. Compared with LAS, BZA has demonstrated reduced mammary stimulation and no evidence of uterine stimulation[33,34].

Historically, the majority of preclinical results have generally been predictive of clinical findings. In phase-3 clinical trials, RLX, LAS, and BZA have all shown significant reductions in the risk of vertebral fracture, increases in BMD, and reductions in markers of bone turnover[37,47,51,56,76]. The incidence of non-vertebral fractures with RLX 60 mg was similar to that with placebo in the overall population[37]; a significant reduction with RLX 60 mg was only seen in a population of women with the most severe prevalent fractures at baseline[43]. A small and clinically irrelevant increase in endometrial thickness was seen with RLX 60 mg compared with placebo, but there was no effect on endometrial carcinoma or hyperplasia. The incidence of non-vertebral fractures was only significantly reduced with LAS 0.5 mg compared with placebo at 5 years in the overall population[47]. Some endometrial safety findings with LAS include a small but significant increase in endometrial thickness and an increased incidence of endometrial polyps[47,49]. BZA 20 mg has shown a significant reduction in the risk of non-vertebral fractures compared with placebo and RLX 60 mg in a *post hoc* analysis of a subgroup of women at higher risk of fracture (baseline femoral neck BMD *T*-score ≤ -3.0 and/or at least one moderate or severe vertebral fracture or at least two mild fractures)[51]. There were no increases in endometrial hyperplasia, carcinoma, or thickness with BZA compared with placebo[51,54,58]. VTE and hot flushes are class effects that have been associated with all SERMs[38,47,48,51,54]. Finally, recently postmenopausal women at increased risk of fracture who also have vasomotor symptoms may benefit from treatment with BZA/CE, which has been shown to significantly increase BMD and also substantially decrease the incidence of hot flushes.

Over the years, SERMs have evolved to secure a place in osteoporosis therapy for postmenopausal women. They may be considered as options for women who cannot take or do not wish to take bisphosphonates, for younger women at increased risk of fracture and potentially breast cancer, who expect to remain on treatment for many years, or as part of long-term sequential interventions.

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