Bazedoxifene: the evolving role of third-generation selective estrogen-receptor modulators in the management of postmenopausal osteoporosis

Barry S. Komm and Arkadi A. Chines

Ther Adv Musculoskel Dis
[2012] 4(1) 21–34
DOI: 10.1177/
1759720X11422602
© The Author(s), 2012.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Osteoporosis is a significant public health concern, particularly for postmenopausal women. Current treatment options may not be appropriate for all women. Selective estrogen-receptor modulators (SERMs) are a class of molecules with tissue-selective activity. Bazedoxifene is currently in clinical development for the prevention and treatment of postmenopausal osteoporosis. In a 2-year, phase III, osteoporosis prevention study ($N = 1583$), bazedoxifene 10, 20, and 40 mg was shown to preserve bone mineral density and decrease biochemical markers of bone turnover compared with placebo in postmenopausal women at risk for osteoporosis. In a pivotal 3-year, phase III, osteoporosis treatment study ($N = 7492$), bazedoxifene 20 and 40 mg significantly reduced the incidence of new vertebral fractures compared with placebo ($p < 0.05$ for both) in postmenopausal women with osteoporosis. In a *post hoc* subgroup analysis of women at higher risk for fracture ($n = 1772$), bazedoxifene 20 mg significantly reduced the risk of nonvertebral fractures *versus* placebo ($p = 0.02$) and raloxifene 60 mg ($p = 0.05$). Bazedoxifene 20 mg has demonstrated sustained efficacy in reducing the risk of vertebral fractures over 5 and 7 years. Overall, bazedoxifene was generally safe and well tolerated, with favorable endometrial and breast safety profiles. As with other SERMs, the rate of deep vein thrombosis was higher in the bazedoxifene groups compared with placebo at 3 and 5 years. Considering its demonstrated efficacy and safety, bazedoxifene may be an appropriate osteoporosis therapy for women who cannot take or are unwilling to take bisphosphonates because of safety or tolerability issues. Bazedoxifene may also be appropriate for younger women at increased fracture risk who are concerned about the effects of long-term bisphosphonate therapy. This article reviews the results of key clinical trials of bazedoxifene for the prevention and treatment of postmenopausal osteoporosis and describes its role in clinical practice.

Keywords: bazedoxifene, fracture, osteoporosis, postmenopausal women, selective estrogen-receptor modulator, treatment

Introduction

Osteoporosis-related fractures are a significant public health concern that contribute to considerable costs both economically and in terms of morbidity and mortality [National Osteoporosis Foundation, 2010]. It has been estimated that 9 million new osteoporotic fractures occurred globally each year [Johnell and Kanis, 2006]. Postmenopausal women are at increased risk of osteoporosis due to a decline in the production of endogenous estrogens

[Gambacciani and Vacca, 2004], which may lead to increased bone remodeling, disordered bone architecture, and an increased risk of fractures [National Osteoporosis Foundation, 2010]. Currently approved pharmacologic prevention and/or treatment options for osteoporosis include bisphosphonates, estrogens, selective estrogen-receptor modulators (SERMs), parathyroid hormone, calcitonin, strontium ranelate (outside of North America), and denosumab [Amgen, 2010a, 2010b; North American

Correspondence to:
Arkadi A. Chines, MD
Pfizer Inc, 500 Arcola
Road, Collegeville, PA
19426, USA
arkadi.chines@pfizer.com
Barry S. Komm, PhD
Pfizer Inc, Collegeville, PA,
USA

Menopause Society, 2010]. Despite the availability of numerous therapies, many women at risk for or diagnosed with osteoporosis are not receiving appropriate therapy [National Osteoporosis Foundation, 2010].

SERMs are a class of molecules that exhibit estrogen receptor (ER) agonist or antagonist activity depending on the tissue they are targeting. An 'ideal' SERM would act as an ER agonist by exerting a protective effect on bone and improving lipid parameters, while also acting as an ER antagonist by maintaining breast and endometrial safety [Komm and Lyttle, 2001]. Bazedoxifene (BZA) is a novel SERM that is currently being developed for the prevention and treatment of postmenopausal osteoporosis; it was recently approved in the European Union for the treatment of osteoporosis in postmenopausal women at increased risk of fracture [Pfizer, 2011]. BZA was initially chosen for development following a rigorous preclinical selection process designed to identify candidate molecules based on the criteria for an 'ideal' SERM described above [Komm *et al.* 2001]. BZA is chemically distinct from other SERMs [Lewiecki, 2007] and has demonstrated a unique profile in preclinical evaluations [Komm *et al.* 2005]. Ovariectomized rats treated with BZA showed significant increases in bone mineral density (BMD) and compressive bone strength compared with controls [Komm *et al.* 2005]. In morphine-addicted rats, a well accepted preclinical model used to evaluate vasomotor instability [Merchenthaler *et al.* 1998], BZA did not have a vasomotor effect as assessed by changes in the rat's tail temperature. In an immature rat model, BZA did not result in significant increases in uterine wet weight or any histological changes, suggesting that BZA did not have stimulatory estrogenic effects on the uterus. Finally, BZA did not stimulate Michigan Cancer Foundation-7 (MCF-7) cells, a well established ER-positive human breast cancer cells line, and also inhibited stimulation of these cells by 17 β -estradiol [Komm *et al.* 2005].

The objective of this article is to review the key findings from the global clinical studies of BZA, including the two extensions of the pivotal osteoporosis treatment study to 5 and 7 years. We also describe clinical findings of BZA partnered with conjugated estrogens (CEs), a new menopausal therapy known

as a tissue selective estrogen complex (TSEC), and outline the potential role of BZA in clinical practice.

Evidence from clinical trials of bazedoxifene

Phase II studies

Early clinical findings in healthy, postmenopausal women ($N=494$) who were treated with BZA 5 mg for 3 months [Ronkin and Clarke, 2001] demonstrated significant reductions in markers of bone remodeling. In a 6-month study ($N=497$), all doses of BZA evaluated (2.5, 5.0, 10, 20, 30, and 40 mg) were shown to be safe and well tolerated in healthy postmenopausal women [Ronkin *et al.* 2005]. BZA 2.5, 5, 10, and 20 mg were not associated with changes in endometrial thickness from baseline compared with placebo; women treated with BZA 30 or 40 mg had smaller changes from baseline in endometrial thickness than those given placebo. In a 2-year study of postmenopausal Japanese women with osteoporosis ($N=429$), daily treatment with BZA 20 and 40 mg led to significant improvements in BMD at the lumbar spine, total hip, femoral neck, and greater trochanter compared with placebo [Itabashi *et al.* 2011]. BZA 20 and 40 mg were also associated with significant changes from baseline in markers of bone turnover, and both doses were well tolerated.

Phase III osteoporosis prevention study

BZA has been evaluated in two global, randomized, double-blind, placebo- and active-controlled, phase III studies (Table 1). The 2-year osteoporosis prevention study was conducted in healthy postmenopausal women ($N=1583$; mean age, 57.6 ± 6.5 years) who were at risk for osteoporosis, defined as BMD T-score at the lumbar spine or femoral neck between -1.0 and -2.5 or other clinical risk factors [Miller *et al.* 2008]. Women were randomly assigned to daily oral doses of BZA 10, 20, or 40 mg, raloxifene (RLX) 60 mg, or placebo. All women were supplemented daily with 600 mg elemental calcium. Among the intent-to-treat (ITT) population ($n=1434$), all doses of BZA and RLX 60 mg were associated with maintenance of BMD, while placebo showed significant bone loss at all skeletal sites. At 2 years, the mean percent change from baseline in lumbar spine BMD compared with placebo was $1.08 \pm 0.28\%$ for BZA 10 mg, $1.41 \pm 0.28\%$ for BZA 20 mg, $1.49 \pm 0.28\%$ for BZA 40 mg, and $1.49 \pm 0.28\%$ for RLX 60 mg ($p < 0.001$ versus placebo for all). Similar improvements in BMD versus placebo were

Table 1. Study designs for phase III clinical trials of bazedoxifene.

	Osteoporosis prevention study (N=1583) [Miller <i>et al.</i> 2008]	Osteoporosis treatment study (N=7492) [Silverman <i>et al.</i> 2008]
Duration	2 years	3 years, with extensions to 5 and 7 years
Study design	Multicenter, double-blind, randomized, placebo- and active-controlled	Multicenter, double-blind, randomized, placebo- and active-controlled
Treatments	<ul style="list-style-type: none"> • BZA 10, 20, or 40 mg/day • RLX 60 mg/day • Placebo 	<ul style="list-style-type: none"> • BZA 20 or 40 mg/day (40 mg/day discontinued during year 4; women in this group transitioned to 20 mg/day) • RLX 60 mg/day (discontinued after year 4) • Placebo
Inclusion criteria	<ul style="list-style-type: none"> • Generally healthy women • ≥ 45 years of age • ≥ 1 year postmenopausal (natural or surgical) • At risk for osteoporosis (normal or low BMD) <ul style="list-style-type: none"> ◦ For women between 1 and 5 years since menopause, lumbar spine or femoral neck BMD T-score between -1.0 and -2.5 or clinical risk factors ◦ For women >5 years since menopause, BMD T-score between -1.0 and -2.5 and clinical risk factors 	<ul style="list-style-type: none"> • Generally healthy women • 55–85 years of age • ≥ 2 years postmenopausal (natural or surgical) • Diagnosed with osteoporosis <ul style="list-style-type: none"> ◦ BMD T-score between -2.5 and -4.0 without prevalent vertebral fracture ◦ BMD T-score not less than -4.0 with ≥ 1 mild vertebral fracture
Primary endpoint	Percent change from baseline in lumbar spine BMD, as measured by DXA at month 24	Incidence of new radiologically confirmed vertebral fractures at month 36
Secondary endpoints	<ul style="list-style-type: none"> • Percent change from baseline in total hip, femoral neck, and femoral trochanter BMD, as measured by DXA at months 6, 12, 18, and 24 • Changes from baseline in bone turnover markers (serum CTx and OC) at months 3, 6, 9, 12, 18, and 24 • Changes from baseline in lipid parameters • Safety and tolerability, based on adverse event reporting 	<ul style="list-style-type: none"> • Incidence of clinical vertebral fractures, determined by radiographic evaluation at months 6, 12, 24, and 36 • Incidence of nonvertebral fractures, determined by direct questioning at regular clinic visits • Changes from baseline in lumbar spine, total hip, and femoral neck BMD, as measured by DXA at months 6, 12, 18, and 24 • Changes from baseline in bone turnover markers (serum CTx and serum OC) at months 3, 6, and 12 • Changes from baseline in lipid parameters • Safety and tolerability, based on adverse event reporting

BMD, bone mineral density; BZA, bazedoxifene; CTx, C-telopeptide; DXA, dual-energy X-ray absorptiometry; OC, osteocalcin; RLX, raloxifene.

observed at 2 years with all doses of BZA at the total hip ($p < 0.001$) and with BZA 20 and 40 mg at the femoral neck ($p < 0.01$) and femoral trochanter ($p < 0.001$) [Miller *et al.* 2008].

BZA 10, 20, and 40 mg were also associated with significantly greater reductions from baseline in serum osteocalcin and C-telopeptide (CTx) levels compared with placebo ($p < 0.001$) at all time points evaluated through 2 years of treatment. Reductions from baseline in serum osteocalcin at 2 years with BZA 10, 20, and 40 mg and

RLX 60 mg (-21% , -22% , -22% , and -27% , respectively) were significantly lower compared with placebo (-6% ; $p < 0.001$ for all). Similarly, reductions from baseline in the bone resorption marker serum CTx at 2 years with BZA 10, 20, and 40 mg and RLX 60 mg (-25% , -24% , -22% , and -32% , respectively) were significantly lower compared with placebo (-13% ; $p < 0.001$ for all).

BZA also showed improvements in lipid parameters compared with placebo [Miller

Table 2. Efficacy results of the phase III treatment study [Silverman *et al.* 2008].

Endpoint	BZA 20 mg (n = 1886)	BZA 40 mg (n = 1872)	RLX 60 mg (n = 1849)	Placebo (n = 1885)
Incidence of new vertebral fractures, Kaplan–Meier estimate (RRR <i>versus</i> placebo) at 3 years*	2.3% [§] [42%]	2.5% [§] [37%]	2.3% [§] [42%]	4.1%
Incidence of nonvertebral fractures, Kaplan–Meier estimate at 3 years	5.7%	5.6%	5.9%	6.3%
Incidence of nonvertebral fractures in higher-risk subgroup, Kaplan–Meier estimate (RRR <i>versus</i> placebo) at 3 years	4.9% [§] [50%]	6.5% [30%]	8.4% [NR]	9.1%
Lumbar spine BMD, mean change from baseline (SE) at 3 years	2.21% [‡] [0.16%]	2.38% [‡] [0.16%]	2.96% [‡] [0.16%]	0.88% [0.16%]
Serum OC, median change from baseline at 1 year	–37% [‡]	–39% [‡]	–41% [‡]	–21%
Serum CTx, median change from baseline at 1 year	–46% [‡]	–49% [‡]	–55% [‡]	–27%

BMD, bone mineral density; BZA, bazedoxifene; CTx, C-telopeptide; NR, not reported; OC, osteocalcin; RLX, raloxifene; RRR, relative risk reduction; SE, standard error.

*Incidence of new vertebral fractures, Kaplan–Meier estimate (RRR *versus* placebo) at 5 years [Silverman *et al.* 2011]: BZA 20 mg, 4.5%[§] (35%); BZA 40/20 mg, 3.9%[§] (40%); placebo, 6.8%.

[§] $p < 0.05$ *versus* placebo.

[‡] $p < 0.001$ *versus* placebo.

[§] $p < 0.01$ *versus* placebo.

et al. 2008]. Compared with placebo, total cholesterol significantly decreased with BZA 10 and 40 mg ($p < 0.05$), low-density lipoprotein (LDL) cholesterol significantly decreased with all doses of BZA ($p < 0.05$), and high-density lipoprotein (HDL) cholesterol significantly increased with BZA 10 and 20 mg ($p < 0.05$) at 2 years. Triglyceride levels significantly increased from baseline in the BZA 20 and 40 mg groups ($p < 0.001$ *versus* baseline for both), but this was also the case in the placebo group ($p < 0.01$ *versus* baseline), and all values remained within the normal treatment range [Miller *et al.* 2008].

BZA 10, 20, and 40 mg were generally safe and well tolerated. The incidences of adverse events (AEs), serious AEs, and withdrawals due to AEs were similar among women treated with BZA, RLX, or placebo. The incidence of hot flushes in the BZA groups (20–24%) and the RLX 60 mg group (19%) was higher than that in the placebo group (14%; overall $p < 0.05$). There were no cardiovascular safety concerns noted in this study. The incidence of breast cancer ($n = 1$ for BZA 10 mg; $n = 2$ for BZA 20 mg; $n = 0$ for BZA 40 mg; $n = 1$ for RLX 60 mg; $n = 2$ for placebo) was low and similar among treatment groups. None of the BZA doses were associated with significant changes from baseline in mean

endometrial thickness at 2 years, and there were no consensus diagnoses of endometrial hyperplasia or carcinoma in any treatment group [Pinkerton *et al.* 2009a; Miller *et al.* 2008].

Phase III osteoporosis treatment study

The pivotal phase III treatment study of BZA was conducted in healthy postmenopausal women ($N = 7492$; mean age, 66.4 ± 6.7 years) with osteoporosis, defined as BMD T-score at lumbar spine or femoral neck between -2.5 and -4.0 without prevalent vertebral fracture or greater than -4.0 with prevalent vertebral fracture (Table 1) [Silverman *et al.* 2008]. Women were randomly assigned to daily oral doses of BZA 20 or 40 mg, RLX 60 mg, or placebo. All women were supplemented with daily oral calcium (up to 1200 mg) and vitamin D (400–800 IU). Among 6847 women in the modified ITT population, the percentage of women with new vertebral fractures at 3 years (Kaplan–Meier estimates) was significantly lower with BZA 20 mg (2.3%), BZA 40 mg (2.5%), and RLX 60 mg (2.3%) compared with placebo (4.1%; $p < 0.05$; Table 2 and Figure 1). These incidences corresponded to risk reductions relative to placebo of 42% [hazard ratio (HR) 0.58; 95% confidence interval (CI) 0.38–0.89] for BZA 20 mg, 37% (HR 0.63; 95% CI 0.42–0.96) for BZA 40 mg, and 42% (HR 0.58; 95% CI 0.38–0.89)

Figure 1. Incidence of new vertebral fractures at 3 years in the phase III osteoporosis treatment study. Kaplan-Meier fracture rates (%) were determined at 3 years for the incidence of new vertebral fractures in the intent-to-treat population ($n = 6847$). Adapted from [Silverman *et al.* 2008], ©2008 American Society for Bone and Mineral Research, with permission from John Wiley & Sons, Inc. BZA, bisphosphonate; CI, confidence interval; HR, hazard ratio; RLX, raloxifene; RRR, relative risk reduction. * $p < 0.05$ versus placebo. ^{\$} $p = 0.89$ for treatment by prevalent fracture status interaction.

for RLX 60 mg. A subgroup analysis showed that the treatment effect was similar ($p = 0.89$) among women with or without prevalent fracture [Silverman *et al.* 2008].

There was no significant difference among treatment groups in the overall incidence of nonvertebral fractures after 3 years, with incidences of 5.7%, 5.6%, 5.9%, and 6.3% for BZA 20 and 40 mg, RLX 60 mg, and placebo, respectively (Table 2). Nonvertebral fractures were further evaluated in a *post hoc* analysis of a subgroup of women at higher risk for fracture ($n = 1772$), defined as femoral neck T-score of up to -3.0 and/or at least one moderate or severe vertebral fracture or at least two mild vertebral fractures at baseline. In this higher-risk subgroup, BZA 20 mg was associated with a 50% reduction in nonvertebral fracture risk relative to placebo

(HR 0.50; 95% CI 0.28–0.90; $p = 0.02$) and 44% relative to RLX 60 mg (HR 0.56; 95% CI 0.31–1.01; $p = 0.05$; Figure 2). When the data for both BZA treatment groups were combined, the incidence of nonvertebral fractures was 40% lower compared with placebo (HR 0.60; 95% CI 0.37–0.95; $p = 0.03$) [Silverman *et al.* 2008].

Because the reduction in nonvertebral fracture risk for higher-risk women with BZA was shown using a *post hoc* analysis, there are limitations to the interpretation of these results. The efficacy of BZA on fractures in the pivotal phase III study was independently re-evaluated using the Fracture Risk Assessment Tool (FRAX) [Kanis *et al.* 2009; McCloskey *et al.* 2009], an algorithm that calculates the 10-year probability of fracture based on easily obtained clinical risk factors with or without femoral neck BMD [Kanis *et al.*

Figure 2. Incidence of nonvertebral fractures among women at higher risk for fracture at 3 years in the phase III osteoporosis treatment study. Kaplan-Meier fracture rates (%) at 3 years were determined for the incidence of nonvertebral fractures in a subgroup of women at higher risk for fracture ($n=1772$; defined as a femoral neck T-score ≤ 3.0 and/or ≥ 1 moderate or severe vertebral fracture or ≥ 2 mild fractures). Adapted from [Silverman *et al.* 2008], ©2008 American Society for Bone and Mineral Research, with permission from John Wiley & Sons, Inc. BZA, bazedoxifene; RLX, raloxifene; RRR, relative risk reduction. *Relative to placebo. \$Relative to RLX 60 mg.

2008]. These analyses evaluated the effect of BZA on fracture incidence as a function of fracture risk using combined BZA data (20 and 40 mg doses) from the overall study population [Kanis *et al.* 2009; McCloskey *et al.* 2009]. Results showed that the efficacy of BZA increased with increasing fracture probability. The risk of all clinical fractures was significantly reduced with BZA for women with 10-year fracture probabilities at or above 16% (80th percentile of risk); for morphometric vertebral fractures, BZA significantly reduced the risk in women with 10-year fracture probabilities at or above 6.9% (41st percentile of risk) [Kanis *et al.* 2009]. In a similar analysis of nonvertebral fractures based on FRAX, BZA was shown to effectively decrease the risk of nonvertebral fractures in women with a 20% or higher 10-year probability of fracture [McCloskey *et al.* 2009]. These findings provide support for the results of the *post hoc* analysis in the phase III treatment study that showed a significant reduction in nonvertebral fractures in higher-risk women treated with BZA [Silverman *et al.* 2008].

Changes in BMD and bone turnover were also evaluated in the phase III treatment study (Table 2). The mean percent changes from

baseline in lumbar spine BMD at 3 years were significantly greater for BZA 20 mg ($2.21 \pm 0.16\%$), BZA 40 mg ($2.38 \pm 0.16\%$), and RLX 60 mg ($2.96 \pm 0.16\%$) compared with placebo ($0.88 \pm 0.16\%$; $p < 0.001$ for all). Responses at the total hip were also significantly greater for BZA 20 mg ($0.27 \pm 0.12\%$), BZA 40 mg ($0.50 \pm 0.12\%$), and RLX 60 mg ($0.90 \pm 0.12\%$) compared with placebo ($-0.83 \pm 0.12\%$; $p < 0.001$ for all). Markers of bone turnover were significantly reduced in women treated with BZA or RLX *versus* placebo ($p < 0.001$). The median percent reductions from baseline in serum osteocalcin at 1 year for BZA 20 and 40 mg and RLX 60 mg (-37% , -39% , and -41% , respectively) were significantly lower compared with placebo (-21% ; $p < 0.001$ for all). The median percent reductions from baseline in serum CTx for BZA 20 and 40 mg and RLX 60 mg (-46% , -49% , and -55% , respectively) were also significantly lower compared with placebo (-27% ; $p < 0.001$ for all) [Silverman *et al.* 2008].

BZA was associated with lipid profile improvements over 3 years [Christiansen *et al.* 2010]. Total cholesterol and LDL cholesterol were significantly decreased from baseline with BZA 20 and 40 mg and RLX 60 mg ($p < 0.05$ *versus*

placebo), and HDL cholesterol was significantly increased with BZA 20 and 40 mg and RLX 60 mg ($p < 0.05$ versus placebo). Although triglyceride levels significantly increased from baseline in all treatment groups ($p < 0.001$ versus baseline), there were no significant differences among groups.

BZA 20 and 40 mg were shown to be generally safe and well tolerated over 3 years of treatment (Table 3) [Christiansen *et al.* 2010; Archer *et al.* 2009b; Silverman *et al.* 2008]. The overall incidences of AEs, serious AEs, and withdrawals due to AEs were similar among treatment groups. As in the prevention study, the incidence of hot flushes was significantly 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 $p < 0.001$). The incidence of cardiovascular AEs was low and similar among groups. There was no difference among groups in the incidence of stroke (Table 4). There was a significantly higher incidence of deep vein thrombosis (DVT) in the BZA and RLX groups [$n = 8$ (0.4%) for BZA 20 mg, $n = 10$ (0.5%) for BZA 40 mg, and $n = 8$ (0.4%) for RLX 60 mg] compared with the placebo group [$n = 1$ (0.1%); overall $p < 0.05$]. There were numerically fewer breast cancer cases in the BZA groups [$n = 5$ (0.3%) for BZA 20 mg and $n = 4$ (0.2%) for BZA 40 mg] than in the placebo group [$n = 8$ (0.4%)]]; this study was not powered to evaluate statistical significance among these events. The incidences of endometrial carcinoma and endometrial hyperplasia were low and similar among treatment groups [Christiansen *et al.* 2010; Archer *et al.* 2009b; Silverman *et al.* 2008].

Two consecutive 2-year extensions of the 3-year core treatment study have been completed [de Villiers *et al.* 2011; Palacios *et al.* 2011; Silverman *et al.* 2011]. A total of 4216 women were enrolled in the first 2-year extension (years 4–5) [Silverman *et al.* 2011], and 1732 women were enrolled in the subsequent 2-year extension (years 6–7). During the first extension, women receiving BZA 40 mg were transitioned to BZA 20 mg (BZA 40/20 mg group), and women receiving RLX 60 mg were discontinued after 4 years. During the second extension, women who previously received BZA 40 mg in the core study continued to receive BZA 20 mg. Supplementation with elemental calcium (1000–1200 mg/day) and vitamin D (400–800 IU/day) was continued for all women. The significant reduction in new

vertebral fractures with BZA 20 mg was sustained through 5 and 7 years. Reductions in the risk of new vertebral fracture with BZA 20 mg versus placebo, based on Kaplan–Meier estimates, were 35% ($p = 0.014$) and 30% ($p = 0.022$) at 5 and 7 years, respectively. Consistent with the results at 3 years, the incidence of nonvertebral fractures at 5 and 7 years was similar among treatment groups in the overall population. Nonvertebral fracture results at 5 years were further analyzed in a subgroup of women at higher risk of fracture ($n = 1324$) using the same criteria as for 3 years (baseline femoral neck T-score of up to -3.0 and/or at least one moderate or severe vertebral fracture or at least two mild vertebral fractures at baseline). In this higher-risk subgroup, there was a 37% reduction in the risk of nonvertebral fracture with BZA 20 mg ($p = 0.06$); combined BZA data showed a 34% reduction versus placebo ($p = 0.05$) [Silverman *et al.* 2011].

The safety and tolerability profile of BZA at 5 and 7 years was similar to that at 3 years (Table 3) [de Villiers *et al.* 2011; Palacios *et al.* 2011; Christiansen *et al.* 2010]. The overall incidence of AEs, serious AEs, and discontinuations due to AEs was similar among treatment groups at 5 and 7 years. Consistent with what was seen at 3 years, the incidence of hot flushes was significantly greater for women treated with BZA than with placebo at 5 and 7 years ($p < 0.001$). The risk of venous thromboembolic events associated with BZA treatment at 5 and 7 years was similar to the risk at 3 years (Table 4). The rate of DVTs per 1000 women-years at 5 years was significantly higher for women treated with BZA 20 mg (1.4; 95% CI 0.6–2.7) and BZA 40/20 mg (1.8; 95% CI 0.9–3.1) than placebo (0.5; 95% CI 0.1–1.4). BZA was associated with a favorable breast and endometrial safety profile. There was no difference in the incidence of breast cancer among the BZA and placebo groups at 5 years. At 5 years, there was a lower incidence of endometrial carcinoma with BZA 20 mg ($n = 0$) and BZA 40/20 mg ($n = 3$) than with placebo ($n = 6$; overall $p = 0.05$). The change from baseline in endometrial thickness at 5 years was similar for BZA 20 mg (-0.04 ± 0.13 mm), BZA 40/20 mg (0.07 ± 0.13 mm), and placebo (-0.19 ± 0.13 mm).

Other phase III studies

Changes in mammographic breast density were evaluated at 2 years in a subset of women enrolled in the phase III osteoporosis treatment study ($N = 444$) [Harvey *et al.* 2009].

Table 3. Safety results of the phase III treatment study.

	3 years, <i>n</i> [%] [Christiansen <i>et al.</i> 2010; Silverman <i>et al.</i> 2008]			5 years, <i>n</i> [%] [de Villiers <i>et al.</i> 2011]			
	BZA 20 mg (<i>n</i> = 1886)	BZA 40 mg (<i>n</i> = 1872)	RLX 60 mg (<i>n</i> = 1849)	Placebo (<i>n</i> = 1885)	BZA 20 mg (<i>n</i> = 1886)	BZA 40/20 mg (<i>n</i> = 1872)	Placebo (<i>n</i> = 1885)
Any AE	1807 (95.8)	1792 (95.7)	1777 (96.1)	1814 (96.2)	1821 (96.6)	1807 (96.5)	1826 (96.9)
Any serious AE	382 (20.3)	368 (19.7)	344 (18.6)	354 (18.8)	467 (24.8)	439 (23.5)	439 (23.3)
Any discontinuation due to AE	278 (14.7)	280 (15.0)	273 (14.8)	253 (13.4)	317 (16.8)	325 (17.4)	293 (15.5)
Selected AEs							
Myocardial infarction	8 (0.4)	8 (0.4)	6 (0.3)	8 (0.4)	9 (0.5)	10 (0.5)	11 (0.6)
Vasodilatation (hot flushes)*	238 (12.6)	243 (13.0)	222 (12.0)	118 (6.3)	245 (13.0)	251 (13.4)	124 (6.6)
Leg cramps [§]	205 (10.9)	204 (10.9)	216 (11.7)	155 (8.2)	256 (13.6)	249 (13.3)	192 (10.2)
Breast carcinoma	5 (0.3)	4 (0.2)	7 (0.4)	8 (0.4)	10 [‡] (0.5)	9 (0.5)	10 (0.5)
Breast pain	53 (2.8)	45 (2.4)	56 (3.0)	48 (2.5)	57 (3.0)	50 (2.7)	51 (2.7)
Endometrial carcinoma [§]	0	2 (0.1)	2 (0.1)	3 (0.2)	0	3 (0.2)	6 (0.3)
Endometrial hyperplasia	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
AE, adverse event; BZA, bazedoxifene; RLX, raloxifene.							
*Overall <i>p</i> < 0.001 at both 3 and 5 years (chi-square test).							
§Overall <i>p</i> < 0.01 at both 3 and 5 years (chi-square test).							
‡Includes one case with breast lesion present at baseline and diagnosed later on in the study.							
§Overall <i>p</i> = 0.05 at 5 years (chi-square test).							

AE, adverse event; BZA, bazedoxifene; RLX, raloxifene.

*Overall $p < 0.001$ at both 3 and 5 years (chi-square test).[§]Overall $p < 0.01$ at both 3 and 5 years (chi-square test).[†]Includes one case with breast lesion present at baseline and diagnosed later on in the study.[§]Overall $p = 0.05$ at 5 years (chi-square test).

Table 4. Rate of cerebrovascular and venous thromboembolic events in the phase III treatment study.*

	3 years [Christiansen et al. 2010]			5 years [de Villiers et al. 2011]			
	BZA 20 mg [n = 1886]	BZA 40 mg [n = 1872]	RLX 60 mg [n = 1849]	Placebo [n = 1885]	BZA 20 mg [n = 1886]	BZA 40/20 mg [n = 1872]	Placebo [n = 1885]
Stroke (total)							
<i>n</i>	12	14	12	14	16	17	19
Rate per 1000 women-years [95% CI]	2.6 (1.34–4.52)	3.1 (1.70–5.23)	2.6 (1.36–4.59)	3.0 (1.65–5.06)	2.5 (1.4–4.1)	2.7 (1.6–4.3)	3.0 (1.8–4.6)
HR (95% CI)	0.9 (0.40–1.86)	1.0 (0.49–2.17)	0.9 (0.40–1.88)		0.8 (0.43–1.63)	0.9 (0.48–1.77)	
Hemorrhagic							
<i>n</i>	1	1	1	2	1	1	4
Rate per 1000 women-years [95% CI]	0.2 (0.01–1.20)	0.2 (0.01–1.24)	0.2 (0.01–1.22)	0.4 (0.05–1.55)	0.2 (0.0–0.9)	0.2 (0.0–0.9)	0.6 (0.2–1.6)
HR (95% CI)	0.5 (0.05–5.53)	0.5 (0.05–5.70)	0.5 (0.05–5.65)		0.3 (0.03–2.24)	0.3 (0.03–2.28)	
Ischemic							
<i>n</i>	9	12	10	10	12	14	13
Rate per 1000 women-years [95% CI]	1.9 (0.89–3.69)	2.7 (1.38–4.66)	2.2 (1.05–4.02)	2.2 (1.03–3.96)	1.9 (1.0–3.3)	2.2 (1.2–3.8)	2.0 (1.1–3.5)
HR (95% CI)	0.9 (0.37–2.22)	1.2 (0.54–2.87)	1.0 (0.42–2.44)		0.9 (0.42–2.02)	1.1 (0.52–2.35)	
Unspecified							
<i>n</i>	2	1	1	2	3	2	2
Rate per 1000 women-years [95% CI]	0.4 (0.05–1.56)	0.2 (0.01–1.24)	0.2 (0.01–1.22)	0.4 (0.05–1.55)	0.5 (0.1–1.4)	0.3 (0.0–1.2)	0.3 (0.0–1.1)
HR (95% CI)	1.0 (0.14–7.10)	0.5 (0.05–5.74)	0.5 (0.05–5.54)		1.5 (0.25–8.96)	1.0 (0.15–7.31)	
Any VTE							
<i>n</i>	13	13	9	8	15	16	10
Rate per 1000 women-years [95% CI]	2.8 (1.49–4.79)	2.9 (1.54–4.94)	2.0 (0.90–3.74)	1.7 (0.74–3.39)	2.3 (1.3–3.9)	2.6 (1.5–4.1)	1.6 (0.8–2.9)
HR (95% CI)	1.6 (0.68–3.94)	1.7 (0.70–4.07)	1.1 (0.44–2.96)		1.5 (0.68–3.35)	1.7 (0.75–3.63)	
DVT							
<i>n</i>	8	9	7	1	9	11	3
Rate per 1000 women-years [95% CI]	1.7 (0.74–3.40)	2.0 (0.92–3.80)	1.5 (0.62–3.15)	0.2 (0.01–1.20)	1.4 (0.6–2.7)	1.8 (0.9–3.1)	0.5 (0.1–1.4)
HR (95% CI)	8.0 (1.01–64.25)	9.4 (1.18–73.82)	7.1 (0.88–57.95)		3.0 (0.81–11.09)	3.8 (1.05–13.51)	
PE							
<i>n</i>	3	3	4	4	4	3	4
Rate per 1000 women-years [95% CI]	0.7 (0.13–1.89)	0.7 (0.14–1.95)	0.9 (0.24–2.24)	0.9 (0.23–2.20)	0.6 (0.2–1.6)	0.5 (0.1–1.4)	0.6 (0.2–1.6)
HR (95% CI)	0.8 (0.17–3.36)	0.8 (0.17–3.47)	1.0 (0.25–4.08)		1.0 (0.25–4.01)	0.8 (0.17–3.47)	
RVT							
<i>n</i>	2	1	0	3	2	2	3
Rate per 1000 women-years [95% CI]	0.4 (0.05–1.56)	0.2 (0.01–1.24)	0 (0.00–0.66)	0.7 (0.13–1.89)	0.3 (0.0–1.1)	0.3 (0.0–1.2)	0.5 (0.1–1.4)
HR (95% CI)	0.7 (0.11–4.00)	0.4 (0.04–3.32)	0		0.7 (0.11–4.00)	0.7 (0.11–4.10)	
Superficial thrombophlebitis							
<i>n</i>	11	18	13	8	13	21	10
Rate per 1000 women-years [95% CI]	2.4 (1.19–4.25)	4.0 (2.38–6.34)	2.9 (1.52–4.87)	1.7 (0.74–3.40)	2.0 (1.1–3.5)	3.4 (2.1–5.1)	1.6 (0.8–2.9)
HR (95% CI)	1.4 (0.55–3.43)	2.3 (1.01–5.33)	1.7 (0.68–3.99)		1.3 (0.57–2.97)	2.2 (1.01–4.57)	
BZA, bazedoxifene; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; RLX, raloxifene; RVT, retinal vein thrombosis; VTE, venous thromboembolic events.							
*Adjudicated data							

BZA, bazedoxifene; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; RLX, raloxifene; RVT, retinal vein thrombosis; VTE, venous thromboembolic events.
*Adjuncted data.

Women eligible for participation in this study were up to 62 years old, had completed 2 years of treatment with BZA 20 or 40 mg, RLX 60 mg, or placebo, and had mammogram pairs taken at baseline and 2 years. At 2 years, the mean changes from baseline in mammographic breast density for BZA 20 mg (−1.2%), BZA 40 mg (−0.4%), RLX 60 mg (−0.5%), and placebo (−0.2%) were small and not significantly different among treatment groups.

BZA has also been evaluated in a 6-month, randomized, double-blind, placebo-controlled, phase III study of postmenopausal Asian women at risk of osteoporosis ($N=486$; mean age 57.2 years) in China, Korea, and Taiwan [Xu *et al.* 2011]. Women were randomly assigned to daily oral doses of BZA 20 mg or placebo and supplemented with calcium carbonate 600 mg daily. BZA 20 mg was associated with significantly greater lumbar spine BMD (0.41%) compared with placebo (−0.32%; $p<0.01$) at 6 months. Similar results were observed at the femoral neck (−0.08% versus −0.69%; $p=0.014$), femoral trochanter (0.50% versus −0.23%; $p=0.010$), and total hip (−0.03% versus −0.77%; $p<0.001$). At 6 months, the median percent reductions from baseline in serum osteocalcin and C-telopeptide in women treated with BZA 20 mg (−19.2% and −30.6%, respectively) were significantly lower than those in women given placebo (−6.3%, $p<0.001$ and −8.8%, $p<0.001$, respectively). The overall incidence of AEs was similar among the BZA and placebo groups.

The tissue selective estrogen complex

The TSEC is a new menopausal therapy that combines a SERM with one or more estrogens, the goal of which is to optimize the tissue-selective activity of each component. An ideal TSEC would treat menopausal symptoms (e.g. hot flashes, vulvar/vaginal atrophy), prevent osteoporosis, and improve lipid parameters, while maintaining breast and endometrial safety [Komm, 2008]. The first TSEC in clinical development partners BZA with CE. The phase III Selective estrogens, Menopause, And Response to Therapy (SMART)-1 trial evaluated various doses of BZA/CE in generally healthy, postmenopausal women with a uterus [Archer *et al.* 2009a; Lindsay *et al.* 2009; Lobo *et al.* 2009; Pickar *et al.* 2009]. At 2 years, all doses of BZA/CE (BZA 10, 20, or 40 mg/CE 0.45 or 0.625 mg) were associated with significant

improvements in BMD and decreases in bone turnover compared with placebo in women at risk for osteoporosis [Lindsay *et al.* 2009]. Also, treatment with BZA 20 mg/CE 0.45 and 0.625 mg significantly reduced the number and severity of hot flashes at 12 weeks and improved measures of vaginal atrophy at 2 years in subsets of symptomatic women. Lipid parameters were also improved with all doses of BZA/CE [Lobo *et al.* 2009]. In addition to demonstrating efficacy in treating menopausal symptoms and protecting against bone loss, BZA 20 mg/CE 0.45 and 0.625 mg were associated with a low incidence of endometrial hyperplasia and high rates of cumulative amenorrhea, similar to those with placebo [Archer *et al.* 2009a; Pickar *et al.* 2009].

BZA/CE has also been evaluated in other phase III studies (SMART-2, SMART-3 trials) in larger populations of symptomatic postmenopausal women. In the SMART-2 trial ($N=332$) of postmenopausal women with moderate to severe vasomotor symptoms, BZA 20 mg/CE 0.45 and 0.625 mg significantly reduced the number ($p<0.001$) and severity ($p<0.001$) of hot flashes compared with placebo at 12 weeks. More women in the BZA 20 mg/CE 0.45 mg (61%) and BZA 20 mg/CE 0.625 mg (73%) groups than in the placebo group (27%; $p<0.001$) experienced at least a 75% reduction in the number of moderate to severe hot flashes at 12 weeks. BZA/CE was also associated with significantly greater treatment satisfaction ($p<0.001$ versus placebo) and improvements in sleep parameters (time to fall asleep, sleep adequacy, sleep disturbance, and sleep problem indices I and II; $p<0.001$ versus placebo) [Pinkerton *et al.* 2009b]. In the SMART-3 trial ($N=664$) of postmenopausal women with moderate to severe vulvar/vaginal atrophy, BZA 20 mg/CE 0.45 and 0.625 mg significantly increased the percentage of superficial cells ($p<0.01$), significantly decreased the percentage of parabasal cells ($p<0.01$), significantly reduced vaginal pH, and significantly improved vaginal dryness and reports of most bothersome vaginal symptom compared with placebo ($p<0.05$). These findings for the four co-primary endpoints of the SMART-3 trial all indicate improvement in the symptoms of vulvar/vaginal atrophy with BZA/CE [Kagan *et al.* 2010]. Women treated with BZA/CE also had significant improvements from baseline in measures of sexual function and quality of life compared with placebo, and were more satisfied with treatment than with placebo [Bachmann *et al.* 2010].

The role of bazedoxifene in clinical practice

The first-line treatment choice for postmenopausal osteoporosis is generally considered to be a bisphosphonate [North American Menopause Society, 2010]. The efficacy of bisphosphonates in reducing the risk of vertebral and nonvertebral fractures has been clearly demonstrated [Hochberg, 2008], and although head-to-head trials have not been undertaken, analyses conducted using observational databases suggest that the common bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid) generally display similar vertebral antifracture efficacies, though differences have been observed at other skeletal sites (e.g. ibandronate has not been shown to be effective against hip fractures) [Harris *et al.* 2009; Pazianas *et al.* 2009; Silverman *et al.* 2007; Liberman *et al.* 2006]. Bisphosphonates may be administered orally based on several different dosing schedules or intravenously every 3 months or yearly.

Some concerns associated with bisphosphonates, however, may limit their utility for certain women. Oral dosing can be complex, requiring both a pre- and post-dose fast for appropriate absorption, with the post-dose fast in an upright position [Cole *et al.* 2008]. The complex dosing schedules contribute to low rates of compliance and persistence [Silverman and Gold 2008]. Bisphosphonate use may also present significant safety and tolerability concerns for many women. Gastrointestinal intolerability, ranging from mild acid reflux to serious esophageal ulcers, is a common concern [MacLean *et al.* 2008]. Intravenous administration of bisphosphonates may be accompanied by acute phase reaction symptoms, although they are generally mild to moderate in severity and become less frequent with repeated intravenous infusions [Black *et al.* 2007; Bobba *et al.* 2006]. Bisphosphonates have also been associated with reports of acute renal failure [Strampel *et al.* 2007; Bobba *et al.* 2006]. Long-term safety considerations with bisphosphonates include a possible increased risk of atypical fractures [Dell *et al.* 2010; Shane *et al.* 2010; Schneider, 2009] and a possible risk of osteonecrosis of the jaw, particularly among patients with cancer receiving high-dose bisphosphonates for bone metastases [Silverman and Landesberg 2009; Khosla *et al.* 2007; Strampel *et al.* 2007].

SERMs are an appropriate alternative for women who cannot take or choose not to take

bisphosphonates because of the considerations described above. Because women who experience gastrointestinal intolerability with one bisphosphonate are likely to experience similar issues with other bisphosphonates [Ideguchi *et al.* 2008], SERMs such as BZA may be an option for these women. Women who cannot take bisphosphonates due to renal insufficiency may be candidates for SERMs. SERMs may also be appropriate for women who cannot adhere to the dosing requirements for bisphosphonates.

Clinical data to date indicate that BZA, which has demonstrated a favorable efficacy and safety profile over 7 years, may be an appropriate pharmacological therapy for certain women. Based on its efficacy on nonvertebral fractures as seen in subgroup analyses, BZA may be considered a first-choice treatment in younger women at increased risk of fracture, particularly those who are likely to remain on therapy for many years and may be concerned about the long-term safety of bisphosphonates. Findings from the *post hoc* analysis of nonvertebral fracture data from the phase III osteoporosis treatment study [Silverman *et al.* 2008] are consistent with the results of the independent reanalyses based on FRAX [Kanis *et al.* 2009; McCloskey *et al.* 2009]. Together, these data provide support for the efficacy of BZA in women who are at higher risk of fracture based on known skeletal risk factors.

Conclusions

Osteoporosis presents a significant public health challenge. As the population of postmenopausal women increases, the development of new treatment options for osteoporosis is becoming increasingly important. BZA is a promising therapy for postmenopausal osteoporosis based on its favorable safety and tolerability profile and efficacy in preventing bone loss and fractures. SERMs such as BZA may be an appropriate therapy for women who cannot or choose not to take bisphosphonates due to gastrointestinal intolerability, safety concerns, or contraindications. SERMs may also be appropriate for younger women at increased risk of fractures who expect to remain on therapy for many years. BZA has also been paired with CE (TSEC) for the prevention of osteoporosis and treatment of menopausal symptoms. Considering its favorable safety and tolerability profile with demonstrated efficacy in preventing fractures, the role of BZA among

currently available osteoporosis treatments is emerging.

Acknowledgments

Medical writing support for this manuscript was provided by Katie Gersh, PhD, of MedErgy. The authors retained full editorial control over the content of the article.

Funding

Funding for editorial assistance was provided by Pfizer Inc, Collegeville, PA.

Conflict of interest statement

Drs Komm and Chines are employees of Pfizer Inc.

References

Amgen. (2010a) Prolia (denosumab) solution for injection. Package insert, The Netherlands: Amgen Europe BV.

Amgen. (2010b) Prolia (denosumab) injection for subcutaneous use. Package insert, Thousand Oaks, CA: Amgen Inc.

Archer, D.F., Lewis, V., Carr, B.R., Olivier, S. and Pickar, J.H. (2009a) Bazedoxifene/conjugated estrogens (BZA/CE): incidence of uterine bleeding in postmenopausal women. *Fertil Steril* 92: 1039–1044.

Archer, D.F., Pinkerton, J.V., Utian, W.H., Menegoci, J.C., de Villiers, T.J., Yuen, C.K. *et al.* (2009b) Bazedoxifene, a selective estrogen receptor modulator: effects on the endometrium, ovaries, and breast from a randomized controlled trial in osteoporotic postmenopausal women. *Menopause* 16: 1109–1115.

Bachmann, G., Bobula, J. and Mirkin, S. (2010) Effects of bazedoxifene/conjugated estrogens on quality of life in postmenopausal women with symptoms of vulvar/vaginal atrophy. *Climacteric* 13: 132–140.

Black, D.M., Delmas, P.D., Eastell, R., Reid, I.R., Boonen, S., Cauley, J.A. *et al.* (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 356: 1809–1822.

Bobba, R.S., Beattie, K., Parkinson, B., Kumbhare, D. and Adachi, J.D. (2006) Tolerability of different dosing regimens of bisphosphonates for the treatment of osteoporosis and malignant bone disease. *Drug Saf* 29: 1133–1152.

Christiansen, C., Chesnut, C.H. III, Adachi, J.D., Brown, J.P., Fernandes, C.E., Kung, A.W. *et al.* (2010) Safety of bazedoxifene in a randomized, double-blind, placebo- and active-controlled phase 3 study of postmenopausal women with osteoporosis. *BMC Musculoskelet Disord* 11: 130.

Cole, Z., Dennison, E. and Cooper, C. (2008) Update on the treatment of post-menopausal osteoporosis. *Br Med Bull* 86: 129–143.

de Villiers, T.J., Chines, A.A., Palacios, S., Lips, P., Sawicki, A.Z., Levine, A.B. *et al.* (2011) Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled phase 3 trial. *Osteoporos Int* 22: 567–576.

Dell, R., Greene, D., Ott, S., Silverman, S., Eisemon, E., Funahashi, T. *et al.* (2010) A retrospective analysis of all atypical femur fractures seen in a large California HMO from the years 2007 to 2009. *J Bone Mineral Res* 25: 1201.

Gambacciani, M. and Vacca, F. (2004) Postmenopausal osteoporosis and hormone replacement therapy. *Minerva Med* 95: 507–520.

Harris, S.T., Reginster, J.Y., Harley, C., Blumentals, W.A., Poston, S.A., Barr, C.E. *et al.* (2009) Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: the eValuation of IBandronate Efficacy (VIBE) database fracture study. *Bone* 44: 758–765.

Harvey, J.A., Holm, M.K., Ranganath, R., Guse, P.A., Trott, E.A. and Helzner, E. (2009) The effects of bazedoxifene on mammographic breast density in postmenopausal women with osteoporosis. *Menopause* 16: 1193–1196.

Hochberg, M.C. (2008) Nonvertebral fracture risk reduction with nitrogen-containing bisphosphonates. *Curr Osteoporos Rep* 6: 89–94.

Ideguchi, H., Ohno, S., Takase, K., Ueda, A. and Ishigatsubo, Y. (2008) Outcomes after switching from one bisphosphonate to another in 146 patients at a single university hospital. *Osteoporos Int* 19: 1777–1783.

Itabashi, A., Yoh, K., Chines, A.A., Miki, T., Takada, M., Sato, H. *et al.* (2011) Effects of bazedoxifene on bone mineral density, bone turnover, and safety in postmenopausal Japanese women with osteoporosis. *J Bone Miner Res* 26: 519–529.

Johnell, O. and Kanis, J.A. (2006) An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 17: 1726–1733.

Kagan, R., Williams, R.S., Pan, K., Mirkin, S. and Pickar, J.H. (2010) A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. *Menopause* 17: 281–289.

Kanis, J.A., Johansson, H., Oden, A. and McCloskey, E.V. (2009) Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed with FRAX. *Bone* 44: 1049–1054.

Kanis, J.A., Johnell, O., Oden, A., Johansson, H. and McCloskey, E. (2008) FRAX and the assessment of

- fracture probability in men and women from the UK. *Osteoporos Int* 19: 385–397.
- Khosla, S., Burr, D., Cauley, J., Dempster, D.W., Ebeling, P.R., Felsenberg, D. *et al.* (2007) Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 22: 1479–1491.
- Komm, B.S. (2008) A new approach to menopausal therapy: the tissue selective estrogen complex. *Reprod Sci* 15: 984–992.
- Komm, B.S., Kharode, Y.P., Bodine, P.V., Harris, H.A., Miller, C.P. and Lyttle, C.R. (2005) Bazedoxifene acetate: a selective estrogen receptor modulator with improved selectivity. *Endocrinology* 146: 3999–4008.
- Komm, B.S. and Lyttle, C.R. (2001) Developing a SERM: stringent preclinical selection criteria leading to an acceptable candidate (WAY-140424) for clinical evaluation. *Ann N Y Acad Sci* 949: 317–326.
- Komm, B.S., Miller, C.P. and Lyttle, C.R. (2001) Preclinical profile of WAY-140424, a third-generation selective estrogen receptor modulator with an improved therapeutic potential. *J Soc Gynecol Investig* 8(Suppl. 1): 84a.
- Lewiecki, E.M. (2007) Bazedoxifene and bazedoxifene combined with conjugated estrogens for the management of postmenopausal osteoporosis. *Expert Opin Investig Drugs* 16: 1663–1672.
- Liberman, U.A., Hochberg, M.C., Geusens, P., Shah, A., Lin, J., Chattopadhyay, A. *et al.* (2006) Hip and non-spine fracture risk reductions differ among anti-resorptive agents: evidence from randomised controlled trials. *Int J Clin Pract* 60: 1394–1400.
- Lindsay, R., Gallagher, J.C., Kagan, R., Pickar, J.H. and Constantine, G. (2009) Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. *Fertil Steril* 92: 1045–1052.
- Lobo, R.A., Pinkerton, J.V., Gass, M.L., Dorin, M.H., Ronkin, S., Pickar, J.H. *et al.* (2009) Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. *Fertil Steril* 92: 1025–1038.
- MacLean, C., Newberry, S., Maglione, M., McMahon, M., Ranganath, V., Suttrop, M. *et al.* (2008) Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med* 148: 197–213.
- McCloskey, E., Johansson, H., Oden, A., Chines, A. and Kanis, J. (2009) Assessment of the effect of bazedoxifene on non-vertebral fracture risk. *J Bone Miner Res* 24(Suppl. 1), Available at: <http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=6c55b263-692e-4a37-b807-f7a153641564> (accessed 18 October 2010).
- Merenthaler, I., Funkhouser, J.M., Carver, J.M., Lundeen, S.G., Ghosh, K. and Winneker, R.C. (1998) The effect of estrogens and antiestrogens in a rat model for hot flush. *Maturitas* 30: 307–316.
- Miller, P.D., Chines, A.A., Christiansen, C., Hoeck, H.C., Kendler, D.L., Lewiecki, E.M. *et al.* (2008) Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. *J Bone Miner Res* 23: 525–535.
- National Osteoporosis Foundation. (2010) Clinician's guide to prevention and treatment of osteoporosis. Available at: http://www.nof.org/sites/default/files/pdfs/NOF_ClinicianGuide2009_v7.pdf.
- North American Menopause Society. (2010) Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 17: 25–54.
- Palacios, S., Silverman, S., Levine, A.B., Kaufman, J.M., Brown, J.P., de Cicco Nardone, F. *et al.* Long-term efficacy and safety of Bazedoxifene in postmenopausal women with osteoporosis: results of a 7-year, randomized, placebo-controlled study. Presented at the 13th International Menopause Society World Congress on Menopause, 8–11 June 2011, Rome, Italy [abstract 973].
- Pazianas, M., Epstein, S. and Zaidi, M. (2009) Evaluating the antifracture efficacy of bisphosphonates. *Rev Recent Clin Trials* 4: 122–130.
- Pfizer. (2011) Conbriza 20 mg film-coated tablets. Summary of product characteristics. Sandwich, Kent, UK: Pfizer Inc.
- Pickar, J.H., Yeh, I.-T., Bachmann, G. and Speroff, L. (2009) Endometrial effects of a tissue selective estrogen complex containing bazedoxifene/conjugated estrogens as a menopausal therapy. *Fertil Steril* 92: 1018–1024.
- Pinkerton, J.V., Archer, D.F., Utian, W.H., Menegoci, J.C., Levine, A.B., Chines, A.A. *et al.* (2009a) Bazedoxifene effects on the reproductive tract in postmenopausal women at risk for osteoporosis. *Menopause* 16: 1102–1108.
- Pinkerton, J.V., Utian, W.H., Constantine, G.D., Olivier, S. and Pickar, J.H. (2009b) Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. *Menopause* 16: 1116–1124.
- Ronkin, S. and Clarke, L. (2001) TSE-424, a novel tissue selective estrogen, reduces biochemical indices of bone metabolism in a dose related fashion [abstract SU437]. *J Bone Miner Res* 16(Suppl. 1): S413.
- Ronkin, S., Northington, R., Baracat, E., Nunes, M.G., Archer, D.F., Constantine, G. *et al.* (2005) Endometrial effects of bazedoxifene acetate, a novel selective estrogen receptor modulator, in postmenopausal women. *Obstet Gynecol* 105: 1397–1404.

- Schneider, J.P. (2009) Bisphosphonates and low-impact femoral fractures: current evidence on alendronate-fracture risk. *Geriatrics* 64: 18–23.
- Shane, E., Burr, D., Ebeling, P.R., Abrahamsen, B., Adler, R.A., Brown, T.D. *et al.* (2010) Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 25: 2267–2294.
- Silverman, S.L., Chines, A.A., Kendler, D.L., Kung, A.W., Teglbaerg, C.S., Felsenberg, D. *et al.* (2011) Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. *Osteoporos Int*, 21 July [Epub ahead of print].
- Silverman, S.L., Christiansen, C., Genant, H.K., Vukicevic, S., Zanchetta, J.R., de Villiers, T.J. *et al.* (2008) Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J Bone Miner Res* 23: 1923–1934.
- Silverman, S.L. and Gold, D.T. (2008) Compliance and persistence with osteoporosis therapies. *Curr Rheumatol Rep* 10: 118–122.
- Silverman, S.L. and Landesberg, R. (2009) Osteonecrosis of the jaw and the role of bisphosphonates: a critical review. *Am J Med* 122: S33–S45.
- Silverman, S.L., Watts, N.B., Delmas, P.D., Lange, J.L. and Lindsay, R. (2007) Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: the risedronate and alendronate (REAL) cohort study. *Osteoporos Int* 18: 25–34.
- Strampel, W., Emkey, R. and Civitelli, R. (2007) Safety considerations with bisphosphonates for the treatment of osteoporosis. *Drug Saf* 30: 755–763.
- Xu, L., Tsai, K.S., Kim, G.S., Wu, Y., Vincendon, P., Chines, A.A. *et al.* (2011) Efficacy and safety of bazedoxifene in postmenopausal Asian women. *Osteoporos Int* 22: 559–565.

Visit SAGE journals online
<http://tab.sagepub.com>

SAGE JOURNALS
Online