

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*

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ABSTRACT: In this 3-yr, randomized, double-blind, placebo- and active-controlled study, healthy postmenopausal women with osteoporosis (55–85 yr of age) were treated with bazedoxifene 20 or 40 mg/d, raloxifene 60 mg/d, or placebo. The primary endpoint was incidence of new vertebral fractures after 36 mo; secondary endpoints included nonvertebral fractures, BMD, and bone turnover markers. Among 6847 subjects in the intent-to-treat population, the incidence of new vertebral fractures was significantly lower ($p < 0.05$) with bazedoxifene 20 mg (2.3%), bazedoxifene 40 mg (2.5%), and raloxifene 60 mg (2.3%) compared with placebo (4.1%), with relative risk reductions of 42%, 37%, and 42%, respectively. The treatment effect was similar among subjects with or without prevalent vertebral fracture ($p = 0.89$ for treatment by baseline fracture status interaction). The incidence of nonvertebral fractures with bazedoxifene or raloxifene was not significantly different from placebo. In a posthoc analysis of a subgroup of women at higher fracture risk (femoral neck T-score ≤ -3.0 and/or ≥ 1 moderate or severe vertebral fracture or multiple mild vertebral fractures; $n = 1772$), bazedoxifene 20 mg showed a 50% and 44% reduction in nonvertebral fracture risk relative to placebo ($p = 0.02$) and raloxifene 60 mg ($p = 0.05$), respectively. Bazedoxifene significantly improved BMD and reduced bone marker levels ($p < 0.001$ versus placebo). The incidence of vasodilatation, leg cramps, and venous thromboembolic events was higher with bazedoxifene and raloxifene compared with placebo. In conclusion, bazedoxifene significantly reduced the risk of new vertebral fracture in postmenopausal women with osteoporosis and decreased the risk of nonvertebral fracture in subjects at higher fracture risk.

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Key words: osteoporosis, treatment, bazedoxifene, selective estrogen receptor modulator, fracture risk

INTRODUCTION

OSTEOPOROSIS, A DISEASE characterized by compromised bone strength, is an increasingly common public health concern, with the prevalence expected to rise steadily

as the worldwide population continues to age.^(1,2) Approximately 200 million individuals are affected globally, including one third of women between the ages of 60 and 70 yr and two thirds of women ≥ 80 yr of age.⁽³⁾ Postmenopausal women are disproportionately affected and are at increased risk for osteoporosis-related fracture, disability, and mortality.^(4–7) In 1998, the total health care costs associated with hip fracture in Europe was estimated at 9 billion Euros.⁽¹⁾ According to 2005 estimates, >2 million osteoporosis-related fractures occurred in the United States alone, with related health care costs approaching \$17 billion.⁽⁸⁾

Our understanding of the fundamental role of estrogen in maintaining bone homeostasis and the complex mechanisms by which estrogen deficiency contributes to bone loss has increased dramatically over the past decade,^(9–11) which has led to the development of numerous treatment options for women with osteoporosis. Currently available pharmacologic agents for postmenopausal osteoporosis primarily exert their effects by decreasing the rate of bone turnover and preserving or increasing BMD, which is one of many

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Dr Silverman has served on advisory boards for Wyeth and Lilly and on the speakers bureau for Lilly. Dr Christiansen has served as a consultant for Wyeth, Eli Lilly, Roche, Novartis, Novo Nordisk, Procter & Gamble, Groupe Fournier, Besins Escovisco, MSD, Chiesi, Boehringer Mannheim, and Pfizer. Dr Genant has served on speaker advisory boards for Wyeth, Lilly, Roche, Amgen, GlaxoSmithKline, Merck, Bristol-Myers Squibb, Genentec, Organon, Medtronic, GE, Hologic, Scanco, and Servier and is a stockholder of Synarc. Dr Zanchetta has served as a consultant for Wyeth, Eli Lilly, Amgen, Pfizer, NPS, MSD, and Servier and has been a lecturer for Wyeth, Eli Lilly, Pfizer, MSD, and Roche. Dr de Villiers has served as an advisory board member/consultant for Wyeth, Servier, and Novartis. Drs Constantine and Chines are employees of Wyeth. Dr Vukicevic states that he has no conflicts of interest.

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factors that determine fracture risk.^(12,13) Approved therapies for the treatment and/or prevention of postmenopausal osteoporosis include bisphosphonates (e.g., alendronate, risedronate, ibandronate, zoledronate), estrogen therapy, calcitonin, PTH, strontium ranelate (outside the United States), and the selective estrogen receptor modulator (SERM) raloxifene.⁽¹⁴⁾ Although existing therapies for postmenopausal osteoporosis have been shown to be effective, they may not be appropriate for all women because of concerns related to safety and/or tolerability. Combined with the significant impact of postmenopausal osteoporosis on a global scale, the continued development of new therapeutic agents remains an important goal.

Bazedoxifene is a novel SERM that has shown tissue-selective activities to confer favorable effects on bone and lipid metabolism without adversely affecting the uterine or breast tissue.^(15–17) Bazedoxifene has been shown to prevent bone loss and decrease bone turnover without stimulating the endometrium in a 2-yr randomized controlled study in healthy postmenopausal women with normal or low BMD.⁽¹⁸⁾ The objective of this study was to evaluate the safety and efficacy of bazedoxifene in treating postmenopausal women with osteoporosis. Importantly, this was the first osteoporosis treatment trial that used an active comparator (raloxifene), in addition to placebo.

MATERIALS AND METHODS

Study design

This international, multicenter, double-blind, randomized, placebo- and active-controlled phase 3 trial was conducted at 206 sites in Asia-Pacific countries, Canada, Europe, Latin America, South Africa, and the United States. Subjects were randomly assigned to receive bazedoxifene 20 or 40 mg, raloxifene 60 mg, or placebo, taken orally once daily. All subjects received oral daily calcium (up to 1200 mg) and vitamin D (400–800 IU) supplements. Subjects were monitored throughout the 3-yr pivotal study period (4-yr extension study is ongoing), with clinic visits occurring quarterly during the first year and biannually during the second and third years.

Subjects

Generally healthy women between the ages of 55 and 85 yr were eligible for study inclusion if they were at least 2 yr postmenopausal and had osteoporosis, defined as low BMD or radiographically confirmed vertebral fractures. Subjects without prevalent vertebral fracture were required to have lumbar spine or femoral neck BMD T-scores between -2.5 and -4.0 (inclusive), whereas subjects with prevalent vertebral fracture (at least one mild vertebral fracture) were required to have lumbar spine and femoral neck BMD T-scores not worse than -4.0 .

Women were excluded if they had diseases that may affect bone metabolism, conditions that could interfere with bone mineral densitometry, pathologic vertebral fractures, vasomotor symptoms requiring treatment, or serious con-

ditions such as endometrial hyperplasia or carcinoma, abnormal vaginal bleeding, malignancy within 10 yr of the study, endocrine disorders requiring treatment, or untreated malabsorption disorders. Subjects with an active or history of deep vein thrombosis, pulmonary embolism, or retinal vein thrombosis were also excluded, as were subjects with elevated fasting total cholesterol or triglyceride levels (≥ 310 or ≥ 300 mg/dl, respectively). The use of androgens, systemic estrogen (except estriol ≤ 2.0 mg/d), topical estrogen (>3 times/wk), progestogens, SERMs, bisphosphonates, calcitonin, PTH, and cholecalciferol ($>50,000$ IU/wk) was prohibited within 6 mo of screening.

Subjects were assigned to treatment using a computerized randomization/enrollment system, which assigned unique randomization and package numbers. Randomization was stratified by prevalent vertebral fracture status to ensure similar distribution of subjects with and without prevalent vertebral fracture across treatment groups.

In accordance with the ethical principles included in the Declaration of Helsinki, all subjects provided written informed consent before study enrollment. The study protocol (including any amendments) and an informed consent form were submitted to the independent ethics committee or institutional review board at each institution for review and written approval.

Endpoints

The primary endpoint was the incidence of new radiographically confirmed vertebral fractures (T_4 – L_4) among women in the bazedoxifene and placebo groups after 36 mo of treatment. Secondary endpoints included the incidence of clinical vertebral fractures and nonvertebral fractures; changes from baseline in BMD of the lumbar spine, total hip, and femoral neck; and changes from baseline in the levels of biochemical markers of bone resorption (serum type-1 collagen C-telopeptide [CTX]) and bone formation (serum osteocalcin).

Efficacy and safety measures

Thoracolumbar (T_4 – L_4) radiographs were obtained at screening and at 6, 12, 24, and 36 mo or at early termination in subjects who withdrew and >6 mo had elapsed since the last radiograph. Prevalent and incident vertebral fractures were identified using the semiquantitative methodology, as previously reported.⁽¹⁹⁾ If an incident vertebral fracture was identified by semiquantitative methodology, a quantitative morphometry assessment was used to confirm the fracture, which was defined as a decrease in vertebral height of 20% or more and 4 mm or more. In cases of disagreement between the two methodologies, a binary semiquantitative assessment by an independent radiologist was conducted to adjudicate the discordant result. In addition, quantitative morphometry was applied to all on-therapy X-rays in subjects with prevalent vertebral fracture. Clinical vertebral fractures were verified by radiographic evaluation using both semiquantitative and quantitative morphometric assessment approaches.

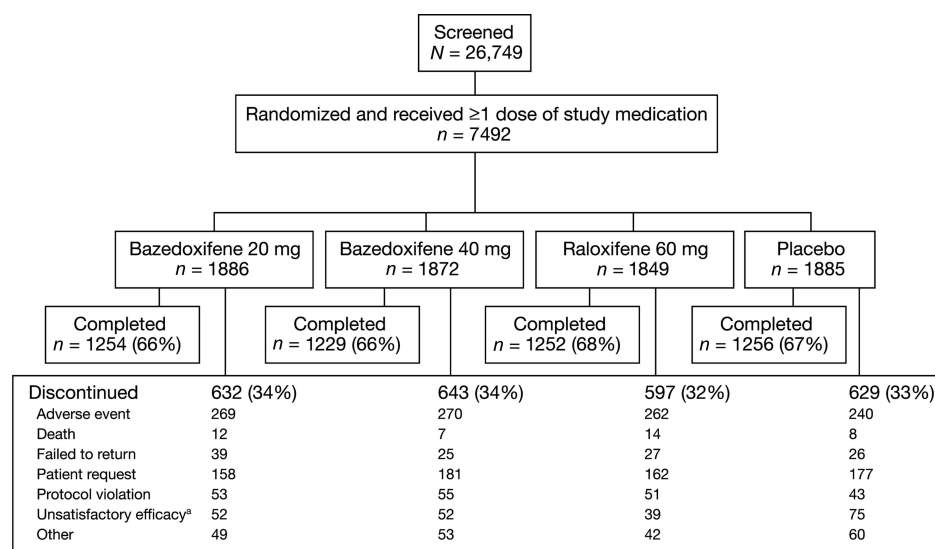


FIG. 1. Disposition of subjects. ^aDefined as the occurrence of a new vertebral fracture or loss of bone mineral density $\geq 7\%$; $p = 0.007$.

Nonvertebral fractures were determined by direct questioning of subjects at each clinic visit. Nonvertebral osteoporosis-related fractures were defined as fractures that were sustained after minimal or low-impact trauma, such as falling from standing height. In addition to the investigator's assessment, all available, pertinent fracture information (e.g., radiology reports, discharge summaries, physician chart notes) was reviewed in a blinded fashion by an independent adjudication board to confirm diagnoses of fracture. Fractures that were pathologic in nature or sustained after significant trauma (e.g., motor vehicle accident, hitting a moving object) were excluded from this analysis, as were fractures of the toes, fingers, face, skull, and elbow, because such fractures were not considered osteoporosis related.

After unblinding of primary data, a posthoc analysis was conducted to evaluate the effect of bazedoxifene on the risk of nonvertebral fracture in a subgroup of women at higher risk for fracture, based on known skeletal risk factors. These skeletal risk factors were low femoral neck T-score (-3.0 or lower) and/or the presence of at least one moderate or severe vertebral fracture or multiple mild vertebral fractures at baseline, consistent with previous reports.^(20,21)

In all subjects, BMD of the lumbar spine and other skeletal sites was measured using DXA at baseline and at 6, 12, 18, and 24 mo; those subjects who consented to participate in the study extension had DXA at 36 mo. All DXA scans and vertebral fracture assessments were evaluated at a central analysis facility (Synarc, San Francisco, CA, USA). Samples for the assessment of serum osteocalcin and CTX were collected at baseline and at 3, 6, and 12 mo and were also analyzed at the central analysis facility (Synarc, Lyon, France).

Safety and tolerability evaluations included adverse event reporting and regular physical examinations and clinical laboratory determinations, including hematology and lipid assessments. Adverse events were classified using the U.S. Food and Drug Administration's Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). Other safety monitoring included regular gynecologic and

breast examinations, cervical cytology smears, transvaginal ultrasound, and endometrial biopsies; the results of these analyses will be described in a separate report.

Statistical methods

The predetermined statistical data analysis plan was developed before study unblinding. Analyses of the primary efficacy data were done using the intent-to-treat (ITT) population, which included all subjects who were randomized to treatment, received at least one dose of study medication, and had undergone vertebral radiography at baseline and at least once during therapy. Subjects who had received at least one dose of study medication were included in the analyses of nonvertebral fracture and safety data.

Sample size calculation was based on the assumption that the incidence of new vertebral fractures over 3 yr would be $\sim 7\%$ in the placebo group. The goal was to enroll a sufficient number of subjects to ensure a total of 1450 subjects per treatment group with at least one on-therapy X-ray assessment. This would provide $\sim 90\%$ power to detect a 40% reduction in the incidence of new vertebral fractures at the 0.05 level (two-sided test).

The cumulative incidence of new vertebral fractures for the ITT population from baseline to 36 mo (primary end-point) was based on Kaplan-Meier estimates. Between-group comparisons were made using the stratified log-rank test; hazard ratios (HRs) and corresponding 95% CIs were constructed from the Cox proportional hazard regression model, adjusted for prevalent fracture status and baseline BMD T-score. The cumulative incidence of nonvertebral fractures from baseline to 36 mo was also based on Kaplan-Meier estimates; between-group comparisons were made using the log-rank test at the 0.05 level. Analyses of nonvertebral fractures were done based on investigator-reported data as recorded in the Case Report Form and also after fracture data had been adjudicated.

Statistical methodology for the posthoc analysis of non-

TABLE 1. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Parameter	Bazedoxifene 20 mg (n = 1886)	Bazedoxifene 40 mg (n = 1872)	Raloxifene 60 mg (n = 1849)	Placebo (n = 1885)
Age (yr)				
Mean (SD)	66.5 (6.5)	66.2 (6.8)	66.4 (6.7)	66.5 (6.8)
Subjects of white ethnic origin [n (%)]	1657 (87.9)	1623 (86.7)	1618 (87.5)	1641 (87.1)
BMI (kg/m ²)				
Mean (SD)	26.6 (3.8)	26.5 (3.9)	26.4 (3.8)	26.3 (3.8)
Time since last menstrual period (yr)				
Mean (SD)	19.7 (8.6)	19.3 (8.9)	19.5 (8.7)	19.5 (8.8)
Natural menopause [n (%)]	1706 (90.5)	1690 (90.3)	1700 (91.9)	1738 (92.2)
Lumbar spine BMD T-score*				
Mean (SD)	-2.4 (1.2)	-2.4 (1.2)	-2.4 (1.2)	-2.4 (1.2)
Femoral neck BMD T-score*				
Mean (SD)	-1.7 (0.9)	-1.7 (0.9)	-1.7 (0.9)	-1.8 (0.9)
Subjects with prevalent vertebral fracture [n (%)]*	967 (56.1)	942 (55.9)	954 (56.3)	981 (56.4)

* Data for intent-to-treat population only.

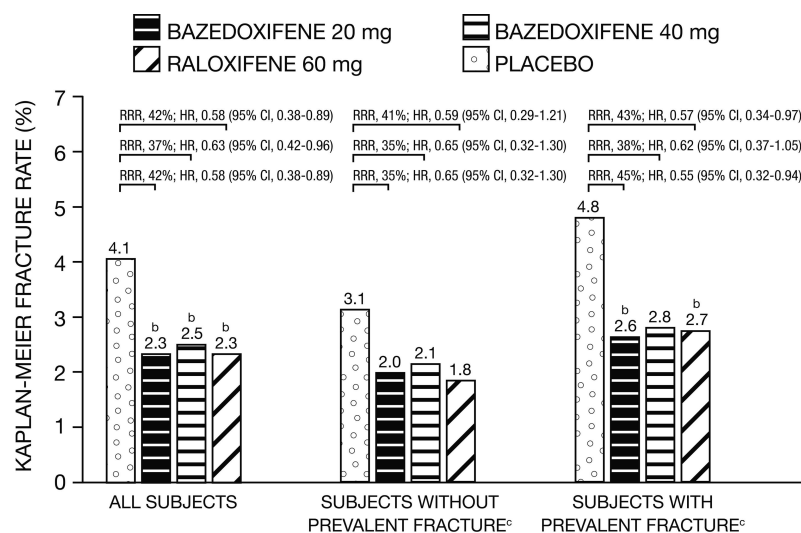


FIG. 2. Incidence of new vertebral fractures and corresponding fracture risk reductions by baseline prevalent vertebral fracture status.^a RRR, relative risk reduction; HR, hazard ratio; CI, confidence interval. ^aIntent-to-treat population; *n* = 6847. ^b*p* < 0.05 vs. placebo. ^c*p* = 0.89 for treatment by prevalent fracture status interaction.

vertebral fractures in subjects at higher fracture risk was similar to that described above. Estimates of HRs and corresponding 95% CIs were obtained using the Cox proportional hazard regression model, adjusted for treatment, baseline fracture status, and femoral neck BMD T-score; between-group comparisons were made using the log-rank test stratified by baseline fracture status.

BMD data were analyzed using an analysis of covariance (ANCOVA) model, which included treatment, prevalent fracture status, and site as terms and baseline BMD as covariate. Summary statistics and between-group comparisons of baseline BMD T-scores were also performed. For markers of bone and lipid metabolism, percent changes from baseline were analyzed using ANCOVA on ranked data with the ranked percent change from baseline as the dependent variable, treatment as factor, and baseline as covariate. Pairwise comparisons were made using *t*-tests, based on the pooled error terms obtained from the ANCOVA. Between-group differences in the incidence of adverse events, serious adverse events, discontinuations because of adverse events, and deaths were evaluated using the Fisher exact test.

RESULTS

A total of 7492 primarily white women (87%) with a mean age of 66.4 ± 6.7 (SD) yr were randomized to treatment and received at least one dose of study medication (Fig. 1). Subject demographic and baseline characteristics were generally similar among treatment groups (Table 1). No differences were observed between treatment groups with regard to age, body mass index, or years since last menstrual period. Adverse events were the most common reason for discontinuation and occurred with comparable frequency across treatment groups (Fig. 1). A significantly higher proportion of subjects who received placebo versus bazedoxifene or raloxifene were discontinued from the study because of unsatisfactory efficacy, defined as the occurrence of a new vertebral fracture or BMD loss of at least 7%.

Vertebral fracture

Baseline and follow-up radiographs were available for 6847 subjects (ITT population for the primary endpoint). The mean T-score was -2.4 ± 1.2 at the lumbar spine and

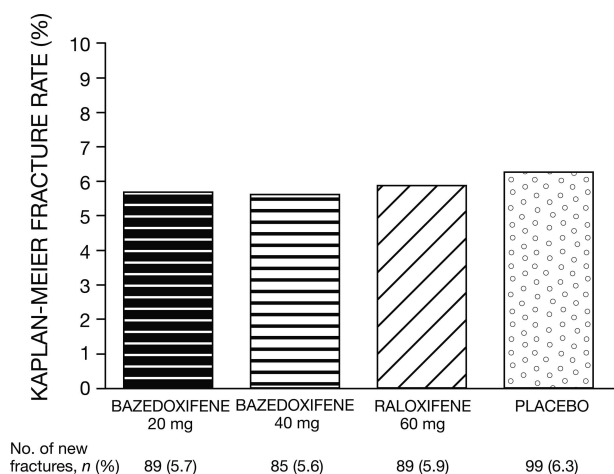


FIG. 3. Incidence of nonvertebral fractures in each treatment group.^a Overall population; $N = 7492$.

-1.7 ± 0.9 at the femoral neck (Table 1). Approximately 56% of subjects in each treatment group had at least one vertebral fracture at baseline, and the majority of these subjects had one mild vertebral fracture. For subjects with or without prevalent vertebral fracture, the mean T-scores were -1.9 ± 1.2 and -3.0 ± 0.7 at the lumbar spine, respectively, and -1.6 ± 0.9 and -2.0 ± 0.8 at the femoral neck.

After 36 mo of treatment, the Kaplan-Meier estimates of the incidence of new vertebral fractures in subjects who received bazedoxifene 20 mg, bazedoxifene 40 mg, raloxifene 60 mg, or placebo were 2.3%, 2.5%, 2.3%, and 4.1%, respectively (Fig. 2). The incidence of new vertebral fractures with bazedoxifene 20 and 40 mg and raloxifene 60 mg was significantly lower ($p < 0.05$) compared with placebo (absolute rate reductions of 1.7%, 1.6%, and 1.7%, respectively). Relative to placebo, bazedoxifene 20 and 40 mg and raloxifene 60 mg significantly reduced the risk of new vertebral fractures by 42% (HR, 0.58; 95% CI, 0.38–0.89), 37% (HR, 0.63; 95% CI, 0.42–0.96), and 42% (HR, 0.58; 95% CI, 0.38–0.89), respectively. There were no statistically significant differences in the incidence of new vertebral fractures among the bazedoxifene and raloxifene treatment groups.

Subgroup analyses of the incidence of new vertebral fractures by baseline fracture status (yes or no) showed that this interaction was not significant ($p = 0.89$), indicating that the treatment effect was similar among subjects with or without prevalent fracture (Fig. 2). The incidence of clinical vertebral fractures was low among treatment groups (bazedoxifene 20 mg, 0.72% [$n = 11$]; bazedoxifene 40 mg, 0.76% [$n = 11$]; raloxifene 60 mg, 0.87% [$n = 13$]; placebo, 0.94% [$n = 14$]), with no significant between-group differences.

Nonvertebral fracture

Overall, there were no significant differences in the incidence of nonvertebral osteoporosis-related fractures among treatment groups (Fig. 3). The incidence of all nonvertebral fractures was 5.7% and 5.6% for the bazedoxifene

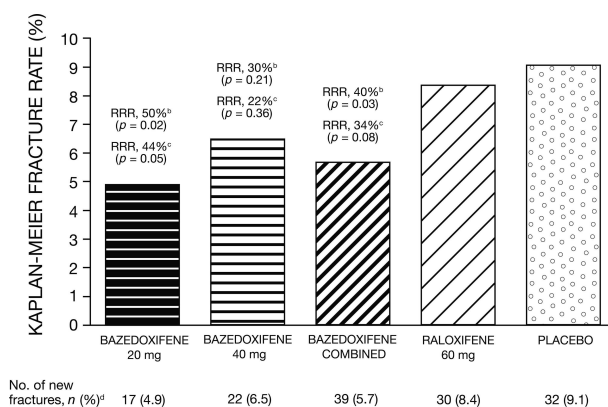


FIG. 4. Incidence of nonvertebral fractures in subjects at higher risk for fracture.^a RRR, relative risk reduction. ^aHigher-risk subgroup (femoral neck T-score ≤ -3.0 and/or ≥ 1 moderate or severe vertebral fracture or multiple mild vertebral fractures); $n = 1772$. ^bRelative to placebo. ^cRelative to raloxifene. ^dMajor fracture sites, n (%): wrist [bazedoxifene 20 mg, 4 (0.8); bazedoxifene 40 mg, 5 (1.2); raloxifene 60 mg, 10 (2.2); placebo, 7 (1.6)]; hip [bazedoxifene 20 mg, 3 (0.7); bazedoxifene 40 mg, 2 (0.5); raloxifene 60 mg, 2 (0.4); placebo, 4 (0.9)]; humerus [bazedoxifene 20 mg, 5 (1.1); bazedoxifene 40 mg, 4 (0.9); raloxifene 60 mg, 7 (1.6); placebo, 3 (0.7)]; lower extremity, including femur, tibia/fibula, patella, ankle, tarsal/metatarsal [bazedoxifene 20 mg, 3 (0.7); bazedoxifene 40 mg, 7 (1.6); raloxifene 60 mg, 6 (1.3); placebo, 17 (3.8)].

20- and 40-mg treatment groups, respectively, compared with 5.9% for the raloxifene 60-mg treatment group and 6.3% for the placebo group.

In a posthoc analysis of a subgroup of women ($n = 1772$) at higher risk for fracture based on known skeletal risk factors, bazedoxifene 20 mg showed a 50% and 44% reduction in the risk of nonvertebral fracture compared with placebo ($p = 0.02$; HR, 0.50; 95% CI, 0.28–0.90) or raloxifene 60 mg ($p = 0.05$; HR, 0.56; 95% CI, 0.31–1.01), respectively (Fig. 4). A lower incidence of nonvertebral fractures was also seen with bazedoxifene 40 mg (6.5%) compared with placebo (9.1%; $p = 0.21$; HR, 0.70; 95% CI, 0.40–1.20) or raloxifene 60 mg (8.4%, respectively; $p = 0.36$; HR, 0.78; 95% CI, 0.45–1.35). Analyses of adjudicated fracture data were consistent with those presented above, which were based on investigator-reported data (data not shown).

The incidence of nonvertebral fractures based on combined data for the two bazedoxifene groups (5.7%) in the higher-risk subgroup was significantly lower compared with placebo (9.1%; $p = 0.03$; HR, 0.60; 95% CI, 0.37–0.95), which corresponded to a 40% reduction in nonvertebral fracture risk (Fig. 4). The combined data for bazedoxifene 20 and 40 mg also showed a trend toward lower incidence of nonvertebral fractures compared with raloxifene 60 mg (8.4%; $p = 0.08$; HR, 0.66; 95% CI, 0.41–1.06).

Data on the incidence of nonvertebral fractures in the lower-risk subgroup (complement of the higher-risk subgroup; $n = 5710$) indicated no significant differences among treatment groups (bazedoxifene 20 mg, 5.9%; bazedoxifene 40 mg, 5.4%; raloxifene 60 mg, 5.1%; placebo, 5.5%).

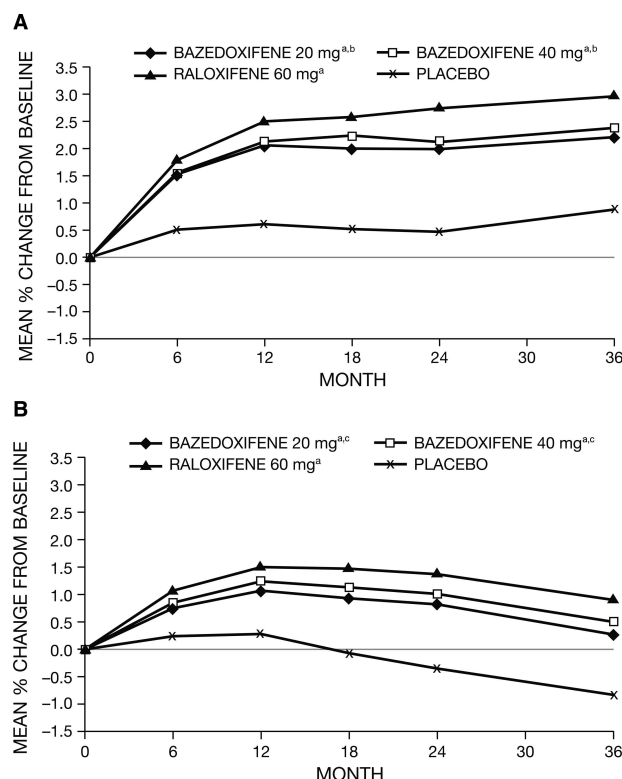


FIG. 5. (A) BMD response at the lumbar spine (L₁-L₄). The mean percent changes from baseline in lumbar spine BMD for the intent-to-treat population (no last observation carried forward) are presented. (B) BMD response at the total hip. The mean percent changes from baseline in total hip BMD for the intent-to-treat population (no last observation carried forward) are presented. BMD, bone mineral density. ^a $p < 0.001$ vs. placebo at each time point. ^b $p < 0.05$ vs. raloxifene at each time point. ^c $p < 0.01$ vs. raloxifene at each time point.

BMD and bone turnover

After 36 mo of treatment, the increase in lumbar spine BMD was significantly greater in the bazedoxifene treatment groups compared with the placebo group ($p < 0.001$; Fig. 5A). Significant treatment effects were apparent within the first 6 mo of therapy in all three active treatment groups and were sustained throughout the study; a small increase was also observed in the placebo group. There were small but statistically significant differences in BMD response at the lumbar spine between the bazedoxifene and raloxifene treatment groups throughout the study ($p < 0.05$). Differences in the mean percent change in lumbar spine BMD from baseline to 36 mo for bazedoxifene 20 and 40 mg and raloxifene 60 mg were $2.21 \pm 0.16\%$, $2.38 \pm 0.16\%$, and 2.96 ± 0.16 (SE), respectively, compared with $0.88 \pm 0.16\%$ for placebo ($p < 0.001$).

Treatment with bazedoxifene 20 and 40 mg was associated with significantly greater increases in BMD of the total hip compared with placebo, which were apparent within 6 mo of treatment and sustained through study end ($p < 0.001$; Fig. 5B). All active treatment groups showed preservation of total hip BMD at 36 mo, whereas significant decreases from baseline in total hip BMD were observed in

the placebo group ($p < 0.001$). There were small but statistically significant differences in BMD response at the total hip between the bazedoxifene and raloxifene treatment groups throughout the study ($p < 0.01$). Differences in the mean percent change in total hip BMD from baseline to 36 mo for bazedoxifene 20 and 40 mg and raloxifene 60 mg were $0.27 \pm 0.12\%$, $0.50 \pm 0.12\%$, and $0.90 \pm 0.12\%$ (SE), respectively, compared with -0.83 ± 0.12 for placebo ($p < 0.001$).

Throughout the study, subjects in the bazedoxifene treatment groups experienced significantly greater reductions in levels of serum osteocalcin and CTX compared with subjects in the placebo group ($p < 0.001$). At 12 mo, bazedoxifene 20 and 40 mg and raloxifene 60 mg significantly reduced median serum osteocalcin levels from baseline by 37%, 39%, and 41%, respectively, whereas placebo showed a 21% reduction ($p < 0.001$). Similarly, bazedoxifene 20 and 40 mg and raloxifene 60 mg significantly reduced median serum CTX levels from baseline by 46%, 49%, and 55%, respectively, whereas placebo showed a 27% reduction ($p < 0.001$). After 12 mo of therapy, there were statistically significant differences in the change in serum levels of osteocalcin and CTX among the bazedoxifene and raloxifene treatment groups ($p < 0.001$).

Safety

Overall, bazedoxifene 20 and 40 mg were well tolerated during the 3-yr core study. Notably, the incidence of adverse events, serious adverse events, discontinuations because of adverse events, and deaths in the bazedoxifene groups were generally similar to that in the placebo group (Table 2). The most common adverse events were abdominal pain, accidental injury, arthralgia, back pain, flu syndrome, headache, hypertension, infection, and pain, each of which were reported by at least 20% of subjects in at least one treatment group. The incidence of vasodilatation (hot flushes) and leg cramps was similar among the bazedoxifene and raloxifene treatment groups and significantly higher than that reported with placebo. Most cases of vasodilatation were mild to moderate in severity and did not lead to subject discontinuation.

The number of cardiovascular events was low and evenly distributed among treatment groups (Table 2). There were no significant between-group differences in the incidence of stroke. No case of ischemic stroke leading to death was reported in the bazedoxifene treatment groups. The incidence of venous thromboembolic events (VTEs; deep vein thrombosis and/or pulmonary embolism) was higher in the active treatment groups compared with the placebo group (bazedoxifene 20 mg, 0.7% [$n = 13$]; bazedoxifene 40 mg, 0.6% [$n = 12$]; raloxifene 60 mg, 0.5% [$n = 10$]; placebo, 0.3% [$n = 5$]). There were no significant differences in the incidence of VTEs among the bazedoxifene and raloxifene treatment groups (Table 2).

There were no significant differences in the incidence of breast cancer among treatment groups, although it occurred with lower frequency in the bazedoxifene treatment groups relative to the placebo and raloxifene 60-mg groups (Table 2). Reports of endometrial carcinoma and endometrial hy-

TABLE 2. OVERALL SUMMARY OF SAFETY PROFILE

<i>Subjects [n (%)]</i>	<i>Bazedoxifene 20 mg (n = 1886)</i>	<i>Bazedoxifene 40 mg (n = 1872)</i>	<i>Raloxifene 60 mg (n = 1849)</i>	<i>Placebo (n = 1885)</i>
Any adverse event	1806 (95.8)	1792 (95.7)	1775 (96.0)	1813 (96.2)
Any serious adverse event	382 (20.3)	368 (19.7)	344 (18.6)	353 (18.7)
Discontinuations caused by adverse event	269 (14.3)	270 (14.4)	262 (14.2)	240 (12.7)
Deaths	17 (0.9)	13 (0.7)	19 (1.0)	11 (0.6)
Selected adverse events				
Myocardial infarction	8 (0.4)	8 (0.4)	6 (0.3)	8 (0.4)
Strokes (total)	19 (1.0)	19 (1.0)	15 (0.8)	20 (1.1)
Ischemic stroke	11 (0.6)	15 (0.8)	9 (0.5)	11 (0.6)
Hemorrhagic stroke	1 (0.1)	1 (0.1)	2 (0.1)	5 (0.3)
Indeterminate*	7 (0.4)	3 (0.2)	4 (0.2)	4 (0.2)
Deep vein thrombosis†	8 (0.4)	10 (0.5)	8 (0.4)	1 (0.1)
Pulmonary embolus	5 (0.3)	3 (0.2)	4 (0.2)	4 (0.2)
Retinal vein thrombosis	2 (0.1)	1 (0.1)	0	3 (0.2)
Vasodilatation‡	238 (12.6)	243 (13.0)	222 (12.0)	118 (6.3)
Leg cramps§	205 (10.9)	204 (10.9)	216 (11.7)	155 (8.2)
Breast carcinoma	5 (0.3)	4 (0.2)	7 (0.4)	8 (0.4)
Breast cyst/fibrocystic breast disease§	13 (0.7)	12 (0.6)	31 (1.7)	18 (1.0)
Endometrial carcinoma	0	2 (0.1)	2 (0.1)	3 (0.2)
Endometrial hyperplasia	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)

Adverse events were classified using the U.S. Food and Drug Administration's Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART).

* Information was insufficient to determine diagnosis.

† Overall $p < 0.05$; χ^2 analysis.

‡ Overall $p < 0.001$; χ^2 analysis.

§ Overall $p < 0.01$; χ^2 analysis.

perplasia were low and similar among treatment groups. A statistically significant difference was observed in the incidence of breast cyst and/or fibrocystic breast disease with raloxifene 60 mg compared with placebo or bazedoxifene.

DISCUSSION

Treatment with bazedoxifene for 3 yr significantly decreased the risk of new vertebral fracture in postmenopausal women with osteoporosis. Relative to placebo, bazedoxifene 20 and 40 mg reduced the risk of new vertebral fracture by 42% and 37%, respectively. Notably, the rates of new vertebral fractures were lower for bazedoxifene compared with placebo across subgroups of women with and without prevalent vertebral fracture. There were no differences in new vertebral fracture rates among the three active treatment groups. The reductions in vertebral fracture risk with active treatment observed in this study are similar to those previously observed in prospective trials of other antiresorptive drugs, including raloxifene and alendronate.^(22–25)

Nonvertebral fractures occurred with similar frequency among treatment groups. Of note, a posthoc analysis in higher-risk subjects showed a significant reduction in nonvertebral fracture risk with bazedoxifene treatment, suggesting a potential benefit in this subgroup of women. These women were at higher fracture risk based on known factors of skeletal fragility, such as low femoral neck BMD and/or prevalent fracture,^(20,21) which select subjects who are most likely to respond to a bone active therapy. Importantly, such clinical risk factors are among those used in a recently developed algorithm for the determination of frac-

ture risk, as supported by the World Health Organization.^(26,27) Among the higher-risk women in this study, bazedoxifene 20 mg showed a significant reduction in the risk of nonvertebral fracture compared with placebo (50%) or raloxifene (44%). The reduction in nonvertebral fracture risk seen with bazedoxifene 40 mg did not reach statistical significance, whereas both bazedoxifene doses had a similar effect on vertebral fractures, BMD, and markers of bone turnover. However, examination of HRs and corresponding 95% CIs around their point estimates did not indicate a difference between bazedoxifene 20 and 40 mg on nonvertebral fracture risk. The latter is also supported by a significant reduction (40%) in the risk of nonvertebral fracture when data for bazedoxifene 20 and 40 mg were combined.

The treatment effect of bazedoxifene on nonvertebral fractures in higher-risk women is overall consistent with that seen in a large risedronate trial, in which a treatment effect on hip fracture was evident only in subjects selected on the basis of skeletal risk factors (i.e., low femoral neck BMD) and absent in those selected on the basis of age and frailty (i.e., propensity to fall).⁽²⁸⁾ Furthermore, the results of a posthoc analysis of nonvertebral fracture data from an ibandronate trial showed a treatment effect in subjects with femoral neck T-score less than -3.0 , but not in the overall study population.⁽²⁰⁾

Bazedoxifene treatment increased BMD of the lumbar spine by $\sim 2\%$, which was apparent within the first 6 mo of treatment and sustained through study end. Such a finding is consistent with that of a recent 2-yr osteoporosis prevention study in healthy, early postmenopausal women.⁽¹⁸⁾ In this study, both bazedoxifene doses showed significantly greater increases in BMD of the lumbar spine and total hip

compared with placebo throughout the treatment period. The small but statistically significant differences in BMD response seen between the bazedoxifene and raloxifene treatment groups in this study are unlikely to be of clinical significance, as supported by a similar reduction in the incidence of new vertebral fractures among the bazedoxifene and raloxifene treatment groups.

Bisphosphonates are known to produce a more pronounced increase in BMD compared with SERMs.^(23–25,29) However, the similar reductions in vertebral fracture rates seen with SERMs and bisphosphonates in non-head-to-head trials indicate that a greater increase in BMD does not necessarily correlate with a greater reduction in fracture risk.⁽³⁰⁾ Indeed, a number of studies have shown that changes in BMD account for only a small portion of the decrease in fracture risk with antiresorptive agents, ranging from 4% with raloxifene treatment to 16–28% with bisphosphonate treatment.^(31–34) In this study, the significant treatment effect of bazedoxifene on the incidence of non-vertebral fractures in higher-risk subjects observed was not seen in the raloxifene treatment group, whereas the effects on BMD and markers of bone turnover were similar overall. Taken together, these findings suggest that other factors, not captured by changes in BMD, may contribute to the reduction in fracture risk with an antiresorptive agent such as bazedoxifene, including reduction in bone turnover and improvement in bone material properties and/or microarchitecture that may enhance bone strength independently from changes in BMD.^(32,35)

Bazedoxifene was generally well tolerated in this population of otherwise healthy postmenopausal women with osteoporosis. The incidence of adverse events, including cardiovascular adverse events, serious adverse events, deaths, and withdrawals because of adverse events with bazedoxifene were similar to that with placebo. A higher proportion of subjects who received bazedoxifene or raloxifene reported vasodilatation and leg cramps; these events, however, were generally mild to moderate in severity and did not lead to subject discontinuation. Similar findings have previously been reported in studies of raloxifene.^(25,36) An increased incidence of VTEs (primarily deep vein thrombosis) was observed in the bazedoxifene and raloxifene treatment groups, a finding consistent with that reported in earlier studies of SERMs.^(25,37) However, the overall incidence of VTEs in the active treatment groups was very low (<1%).

Bazedoxifene was associated with a favorable endometrial safety profile, as evidenced by a low incidence of endometrial hyperplasia or carcinoma similar to that with placebo. The incidence of breast cancer was low in this study. Fewer cases of breast cancer were reported in both bazedoxifene treatment groups compared with the placebo and raloxifene groups, which may indicate a protective effect on breast cancer as has been shown with other SERMs.^(25,37) Furthermore, bazedoxifene was associated with a lower incidence of breast cyst or fibrocystic breast disease compared with placebo or raloxifene.

An important difference between this study and previous clinical trials of postmenopausal women with osteoporosis is the lower incidence of new vertebral fractures observed

in this study, which was 4% in the placebo group. In comparison, the rates of new vertebral fractures reported for placebo-treated subjects have ranged from 10% to 29% in previous 3-yr studies of raloxifene⁽²⁵⁾ and risedronate,⁽³⁸⁾ respectively. The lower incidence of new vertebral fractures observed in this study is consistent with the enrollment of subjects at lower risk for fracture compared with other clinical trials. For example, this study allowed for the enrollment of subjects with one mild prevalent vertebral fracture, whereas other osteoporosis studies have required subjects to have two or more mild prevalent vertebral fractures or one or more moderate or severe prevalent vertebral fracture.^(25,38) It should be noted that the availability of a number of approved osteoporosis treatments at study initiation made the enrollment of subjects at very high risk for fracture unethical, based on updated guidelines contained within the Declaration of Helsinki (October 2000).⁽³⁹⁾ In addition, the higher level of calcium supplementation (1200 mg) may have contributed to the observed fracture reduction because previous osteoporosis trials of similar design have used supplemental calcium levels between 500 and 1000 mg.^(20,23–25,28,38) Nevertheless, both doses of bazedoxifene showed a significant and clinically meaningful reduction in the incidence of new vertebral fractures in this study, supporting the robustness of the treatment effect.

In conclusion, bazedoxifene treatment of postmenopausal women with osteoporosis significantly reduced the risk of vertebral fracture, increased BMD of the hip and spine, and reduced bone turnover. Notably, bazedoxifene treatment also showed a significant reduction in the incidence of nonvertebral fractures in subjects at higher risk for fracture. Both doses of bazedoxifene were generally well tolerated over 3 yr of therapy. Findings from this study suggest that bazedoxifene may be a promising new therapy for the treatment of postmenopausal osteoporosis.

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